Challenges in Technology Transfers of API Manufacturing to India

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The PolyPeptide Group is an international manufacturer of peptide-based active pharmaceutical ingredients with manufacturing facilities in five countries (Denmark – France – India – Sweden –USA) across three continents. The site close to Mumbai in India is newly operational and has finalized the first two all functional product technology transfers from the USA and two are ongoing from Scandinavia. This article outlines some of the challenges as well as the actions taken when transferring product manufacturing from USA and Europe to India

PolyPeptide India at a glance

Location

Ambernath, Maharashtra, India
(60 km Northeast of Mumbai)

Function

Designed for Generic Peptide API Manufacturing

Capacity

Multiple Manufacturing Lines
(Up to multi-kg batch size).
Expansion Capacity: 50%

Production

Solid Phase Peptide Synthesis,
Liquid Phase Peptide Synthesis,
Production scale HPLC/RPC, Lyophilisation

Background

In 2005, the PolyPeptide Group started planning the development of a new manufacturing site in India with the ambition of participating in the rapidly expanding pharmaceutical industry in Asia. The location selected was Ambernath, Northeast of Mumbai, state of Maharashtra, in a newly established industrial area. The company started planning the utilization of a six acre plot of land.

The design and planning of the facility was performed by a group of local and International consultants managed by the PolyPeptide Group internal project steering team. For the construction, the contractors were Indian supervised by a local general consultant and supported by international expertise. The qualification and validation of the facility was managed by the validation departments of the PolyPeptide Group.

After the site inauguration and a period of commissioning, qualification, validation, operational training and technical fine-tuning, the PolyPeptide Group initiated the product technology transfer to the new facility with two generic peptide APIs from one of the existing facilities in the USA. The startup of a new manufacturing facility further cemented the continued ambition of implementing the PolyPeptide best practices at all facilities across the Group. The India project has contributed significantly to the harmonization of the PolyPeptide Group and the primary contributor has been the activities within the product technology transfer.

Technology Transfer Approach

Organization of the multiple process technology transfers to our facility in India are facilitated by a cross-company team which follows progress, addresses challenges, provides and coordinates technical assistance and identifies resource needs from the local organizations. A single person of contact at each site facilitates the local exchange and distribution of information.
The technology transfer process is systematically executed in the PolyPeptide Group by following our global policy for technology transfers. Essential activities include:

- A technology transfer plan: Outlines all transfer activities in great detail.
- Compilation of detailed process information at the receiving unit
- Comparability report: Technical gap analysis exercise between the receiving and sending site. This determines whether key elements such as equipment, raw material specifications and packing materials are like-to-like, comparable or need to be changed or adjusted at the receiving unit.
- Analytical methods transfer
- Preparation of master batch records at the receiving site, which are then reviewed by the sending unit
- Risk assessments: Generates enhanced process understanding
- Training of work force at receiving unit
- Technology transfer report
- Process validation

In addition to the above points, an involvement from the PolyPeptide Group management is arranged. Thus, bi-weekly meetings involving representatives of senior executive management and all involved functions monitor progress and facilitate solutions to problems.

The challenges

Cultural aspects and communication
Technology transfer is a complex process involving several disciplines and with many associated risks that need to be managed. These risks can be more evident within any organisation when transferring manufacturing from one culture to another. In such cases, managing technology transfer and supporting the new manufacturing site can become more complicated due to cultural and organizational differences between the involved sites. In addition, considerable time-zone differences across three continents and, at times, less reliable means of communication, e.g. telephone connections fall out, increase the attention to the need of efficient communication.

Despite of the use of modern technology, e-mails and online meetings, it has been our experience that face-to-face meetings are fundamental in establishing good personal and working relationships at all levels between the involved parties. The face-to-face meetings are efficient if they are well planned, and the added benefit of generating mutual respect for the cultures and the cultural differences cannot be underestimated. Of course, the face-to-face meetings can also present new challenges for personnel from both the transferring and receiving sites.

The interpretation of body language may differ markedly between the different cultures – simple everyday gestures such as nodding or shaking of the head coupled with inactive behavior can be construed as either an affirmative or a negative and in some cases an aggressive response depending on the beholder. Some behaviors are considered correct and even good manners in one culture while being considered faulty in another. There may be differences in the understanding and acceptance of hierarchy, and there may also be differences in the perception of time.

In dealing with these and other similar situations the execution of introductory sessions in cultural differences provided to team members from all associated sites have proven truly beneficial With an increased understanding of each other's culture we are able to create an environment of collaboration, and to minimize and prevent misunderstandings within the team.

Regulatory aspects
The regulatory change associated with a change of the manufacturing site can represent a big challenge to the timelines of the project. Thus, Regulatory Affairs has been involved in the project from the early planning stage. The timeline must not only take into account the updating of PolyPeptide's registration documentation, but also the regulatory activities necessary for the customer, the license holder to submit and obtain regulatory approval for the change of API manufacturing site. An early assessment performed by a global regulatory interface is crucial for determining the overall timelines for the project and each API is considered a separate case. In some cases when PolyPeptide decides to make changes to the manufacturing method, it is essential to be able to show the equivalency between the pre- and post-change material, especially with respect to the impurity profile and stability performance of the API.

Technical aspects
One of the main technical challenges that we were facing during the execution of a technology transfer was to capture the relevant collective knowledge and experience at the sending units and to effectively transfer it to the receiving unit without loss of information. The know-how that is being passed over will form the basis for the manufacturing process, the in-process control strategy, process validation and ongoing continuous improvement. So, our ultimate goal is to transfer the knowledge with sufficient level of detail to ensure that the results previously obtained at the sending unit will be reproduced at PolyPeptide India in a robust manner. This is achieved by compiling the existing process knowledge in detailed protocols and reports and providing PolyPeptide India with detailed manufacturing instructions and process description. Elements such as material of construction of equipment and utensils, type of filters or stirrers and dimensions of equipment are examined. Care is also taken in evaluating that parameters like temperature and stirring ranges of the equipment are matching the process requirements.

Despite these efforts, for one of our products we faced an investigational situation in the first non-GMP batch manufactured at the Indian site as the QC testing showed that the product exceeded the limit of phosphate content. The root cause investigation that was conducted concluded that the problem was neither in the process nor in the execution of operations but equipment related. Even if an initial assessment of equipment was made, which concluded adequate performance, the complexity of the piping of the HPLC preparative equipment at our site in India was underestimated. A number of horizontal and vertical short dead legs held a volume that was different from the equipment at the sending unit which, in fact, had a minimum path length. In conclusion, the presence of the short dead legs was the physical cause of phosphate buffer substance from a previous purification step not being effectively removed with the specified wash volumes and thus inadvertently being carried over into the product. As a corrective action the equipment was modified by blinding the dead legs and shortening the path, and no reoccurrence has been observed since. This example emphasizes that attention to detail is the key to a successful implementation of manufacturing at the receiving site. It also tells that engineering runs, which are meticulously investigated for any flaw or defect are a well-invested activity. The assembly of all process details is without doubt one of the most laborious, time and resource consuming activity in the tech transfer process, and care must be taken not to underestimate this task and the elements therein.

Based on the process information available at the sending unit and prior to initiating the transfer a technical assessment is performed where it is determined whether adjustments or changes need to be implemented at the receiving unit. In such cases, the need for a non-GMP engineering run is more evident. We do this at PolyPeptide India in order to confirm the process, the changes and to fine-tune the process execution before the start of the GMP manufacturing. Evidently, this has the further benefit of being efficient training in both manufacturing process and in-process methods. In the case of transfer of a process from PolyPeptide USA, some changes needed to be implemented in the lyophilization step as a different type of lyophilizer was used at the receiving unit. This triggered lyophilization development activities in PolyPeptide Scandinavia and a few trial runs at PolyPeptide India with the commercial-scale lyophilizer before implementation.
In a number of processes, the technology transfer activities have been the perfect opportunity for bringing the older processes up to today's standards and expectations in regard to safety and environment by exchanging diethyl ether with much less toxic and more safe solvents

Analytical method transfer
As the activities related to analytical method transfer are many and time consuming, the information is communicated to PolyPeptide India early in the project in order to facilitate the initial method testing, preparation of the method description and the necessary SOP's. Purchase of reagents, solvents, analytical columns also needs to be carried out prior to the method transfer. All the pre-transfer efforts will later contribute to streamline the method transfer.
Site-specific operating procedures are another factor that needs to be examined early in the process since additional testing may be needed in order to demonstrate suitability and this can potentially delay the implementation of the method. Like in all transfer of knowledge, for analytical method transfers and particularly for chromatographic methods, care must be taken that details such as analytical column type, oven temperature and buffer preparations are well documented. Further to this we have found of vital importance to scrutinize integration software set-ups and integration routines in order to ensure equivalency.

If the analysis of a product requires equipment currently not available at PolyPeptide India, the PolyPeptide Group benefits from the availability at other sites. In this case, the other sites would operate as contract laboratories.
The occurrence of a potential analytical problem in a non-GMP batch from PolyPeptide India triggered a root cause investigation. The investigation indicated that not all details of potential water uptake in samples were clear, which, in turn, made us look further into the way we send and plan analysis of samples across sites. A specific, pre-defined packaging configuration was then investigated by sending samples back and forth and analyzing them for water uptake. The outcome of this investigation showed that no water uptake occurred using the packaging configuration, thus allowing us to decide where the sample should be analysed for water. In this case, it was decided that water should be analyzed at the same laboratory as the amino acid analysis.

Training
Technical training of the workforce at PolyPeptide India has been and continues to be an important activity and a key to success. The initial assessment of the manufacturing process defines whether equipment, analytical, or process-specific training is needed, which often necessitates the relocation of personnel from one site to the other for a select period of training. This has resulted in several training activities including, amongst others:

- Production chemists from PolyPeptide India have been trained at PolyPeptide USA where they observed the execution of the GMP manufacture of the product that was to be transferred.
- Analyical chemists were sent to PolyPeptide USA to be comprehensively trained in the establishment of intricate analytical HPLC release methods.
- Prior to the implementation of the ultrafiltration technology at PolyPeptide India, a member of the technical team from PolyPeptide USA joined the PolyPeptide India team to assist in qualification of the equipment and provide invaluable on-site training.

Further to this, continuous technical support from the sending unit and the core-team is facilitating the transfer and sustaining product manufacturing (troubleshooting, analysis, documentation review, technical meetings).

Raw/packaging materials
Raw material specifications are usually a critical issue during a technology transfer and the total of activities required is time-consuming: preparation of raw material specifications, qualification of suppliers and implementation of analytical methods at receiving unit. All these activities are significantly less complex at PolyPeptide after the implementation of global specifications and supply for the most commonly used amino acid derivatives. For materials other than amino acids (solvents and reagents) the quality provided by local suppliers needs to be evaluated against the incoming material specification used in the design of the process. For these materials, delays in supply from the local vendor can be critical for the transfer.
For packaging materials, we have found in two cases that the same supplier has been much less responsive to the orders and requests coming from our facility in India compared to what we are used to in other PolyPeptide sites. This is causing us delays in the purchase and potentially in the project.

Process validation
Although the company has made great strides in the process of harmonization and globalization, some of the older processes may have been developed following different standards. In these cases, technology transfer contributes to increasing process understanding and the critical parameters: risk assessment tools have been implemented in order to identify gaps of process information or data and helped in defining the studies to be performed in the first batches at PolyPeptide India. Later on, prior to process validation, a revised risk assessment is performed with focus on determination / confirmation of the critical process parameters.
Process validation is the ultimate step in the process of technology transfer and it will reflect how successfully the transfer of knowledge has been performed. The process validation is grounded on historical data from previous runs at the sending unit as well as test and registration runs at PolyPeptide India. Securing a robust process validation is a difficult task and focus on this aspect from the early stage in the technology transfer is necessary in order to succeed.

Organizational aspects
From the organizational point of view the main challenge at the sending units is to balance the resources between the local, site-specific projects and the technology transfer projects. In our experience it is essential for the success of the transfer that the use of resources in the involved sites is transparent, acknowledged and authorized by local and global management. In our case the involvement of senior management in bi-weekly meetings with all disciplines present (operations, QA, RA, SM) facilitates the prioritization and allocation of resources from different departments across sites.

GMP certification
Having PolyPeptide India GMP-certified is another key success parameter. In collaboration with the authorities we have planned and now received final confirmation that an inspection will take place before the end of this year.

Conclusion

We believe that our technology transfer to India has been and continues to be successful. The success, however, has not come without the significant efforts of many people in the technology transfer teams. Our key learning's learning curve have includes been dealing with theunderstanding of the culturescultural differences, learning to deal with theattention to details, dealing with the problems, take taking nothing for granted, create creating awareness by publishing the results, and always keeping an open mind. In reward, we have the opportunity to participate in one of the most interesting, educating and challenging efforts happening today in a globalized world, and thereby helping to maintain the PolyPeptide Group as a world leader in pharmaceutical peptide manufacturing.