6.2 Manufacturing Process Transfer

6.2.1 Overview of Manufacturing Process Transfer

The installation of the manufacturing process for a recombinant protein-based vaccine occurred through two different TTPs. The initial technology transfer from the R&D unit to the manufacturing unit (development to commercialization TTP) resulted in the manufacturing of lots that were used in Phase 3 clinical trials and for launch supply. After this initial TTP, a second TTP was conducted (intra-company TTP) to a scaled-up purification facility which was required to meet the projected market supply requirements.

The manufacturing process consists of yeast-based fermentation, purification, and reassembly of the recombinant protein virus-like-particles (VLPs); adsorption to an adjuvant; and sterile formulation and filling. Key challenges during process development included protein expression in a defined media fermentation and control of VLP aggregation and stability.
These challenges were overcome via the TTP to produce a small-scale process suitable for early phase clinical testing.

6.2.2 Case Description: Development to Commercialization TTP

The TTP was initiated with a facility fit analysis to compare the unique aspects of the processing equipment in the existing fermentation facility to the process as defined in R & D. This led to targeted development work to better fit the process into the intended manufacturing facility. For example, the relative scale of the fermentation seed process was modified and tested to fit into the fixed equipment in the existing facility. In addition, some facility changes were required to meet the needs of the process. A new purification facility was required, and close collaboration between the R&D and manufacturing units led to an agile design that met the processing needs. Finally, the formulation and filling process was transferred to an existing facility.

A risk assessment was performed to characterize the process parameters and attributes. The product's CQAs were identified，and the process experts determined the associated CPPs that were responsible for controlling the CQAs.

Other attributes that were important for process consistency (key product attributes and operating parameters) were also identified to further define the manufacturing process. The ranges associated with these attributes and parameters were determined experimentally. However, in most cases, the limits were known "success" values rather than those at the boundary of failure due to the complexity of the process and product. The ranges were approved by the R&D unit and the manufacturing organization (operations, quality, and technical operations) and were the basis for process validation. The ranges for CQAs and CPPs were maintained for all components, except that some were changed due to process scale and planned

process changes.

A well-defined business process existed in the enterprise and was used to organize and manage the TTP for the product. The features of the business process included:

Formation of a technology transfer team that was responsible for executing the technology transfer plan. Members of this team included representatives of R&D, operations, quality, technical operations, and regulatory units.

Appointment of a technology transfer leader who was responsible for organizing and managing the team and reporting progress to a governing authority.

A governance team of cross-functional leaders that oversaw the technology transfer plan and served as a decision-making body when issues were encountered. The team chartered the project and team and oversaw the project using a "stages and gates" approach. Stages are logical groups of associated activities and tasks that are part of a TTP. Stage gates are review points that are defined in advance by the governance team and focus on project status, key milestones for the next stage, and, importantly, the risks and risk mitigation plans for the project. For example, production of process validation lots was considered a distinct stage, and a stage gate review was conducted by senior leadership to ensure readiness for the process validation series and communication of the potential risks to the process validation lots.

A project management system used to ensure sound project definition and execution control. During the initiation and planning stage, a project plan was produced and was reviewed by the governance team. The plan resulted in approved schedule milestones that the technology transfer team was expected to meet. This stage also included definition of key assumptions and project risks that governed the project plan.

An execution stage consisting of process readiness in the manufacturing facilities (for example, IQ /OQ and engineering lots), completion of process validation lots, and licensure of the facilities.

The process validation lots were used in Phase 3 clinical trials, which conclusively demonstrated the successful transfer of the process technology form the R&D to the manufacturing unit. Approval of the manufacturing facilities occurred concomitantly with product regulatory approval.

6.2.3 Intracompany TTP

To limit the capital expenditures before obtaining critical clinical performance data, a small-scale purification facility was used as the initial manufacturing facility to produce process validation lots used in the Phase 3 clinical studies and to manufacture drug substance for product launch. However, the expected market demand exceeded the capacity of the launch facility. Consequently

a scaled-up purification facility was constructed.

The process for the new facility was scaled up, which required targeted process changes to manage the larger production scale. For example, filter configurations were changed to reflect limitations in mechanical equipment design. In addition, a planned material manufacturing change by the vendor was evaluated in R&D to ensure success in the new factory.

A project team was assembled in the manufacturing organization for the startup of the new facility and technology transfer from the initial purification facility. This team had a similar structure to that described above, although it was based at the manufacturing site. A governance team oversaw project execution and was responsible for rapid decision-making and resolution of issues escalated by the project leader. A communication plan was defined and implemented to ensure alignment in the organization concerning project implementation.
Because the drug substance was a recombinant protein that was considered a well-characterized biologic, a comparability approach was taken for licensure of the new purification facility. This approach was aligned with the guidance in ICH Q5E Comparability of Biotechnological/Biological Products subject to Changes in their Manufacturing Process and provide a framework for evaluating the impact of the process changes and scale-up on product safety and quality (22).

A summary of the business process deployed for comparability is shown in Figure 6.2.3.1. Comparability consisted of demonstration of both process performance measures (e.g., key process attributes) and product quality attributes (e.g., product specifications). The expected results for these measures were defined by statistical analysis from production lots made in the launch facility. A weighing approach was used for the analytical measures to account for the relative importance of test results; for example, due to its impact on product quality the potency test was considered a more important measure than the characterization test.

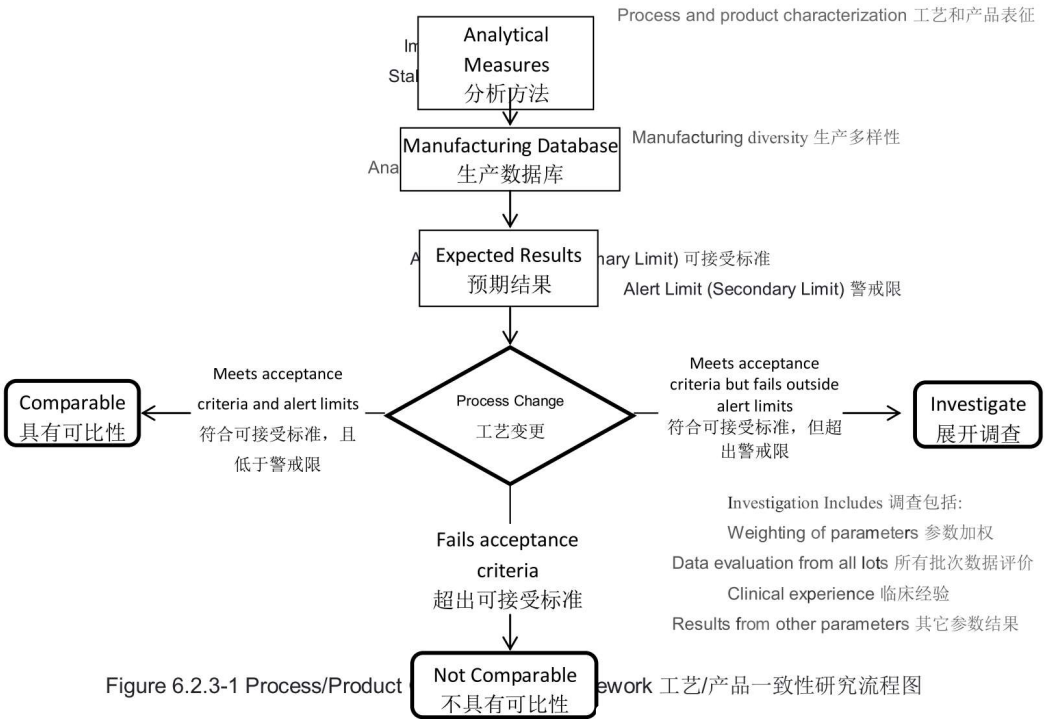

Figure 6.2.3-1 Process/Product ework 工艺/产品一致性研究流程图

The process validation lots made in the new purification facility were tested according to the requirements in the comparability protocol. All lots made were deemed to be comparable to the small-scale launch facility, which led to the successful licensure of the facility without clinical studies.

6.2.4 Conclusion

A successful production history lasting more than five years after licensure demonstrates the success of the technology transfer process used for this product.

Reference: PDA TR 65