Know-how Technology Transfer from R&D to Manufacturing

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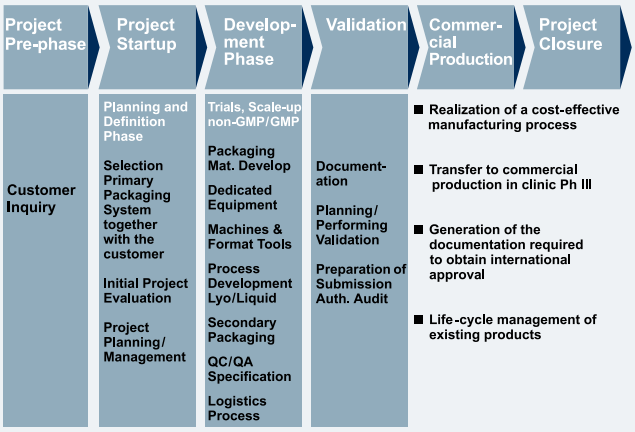
Introduction

Each product needs to be transferred from R&D scale to commercial manufacturing scale. This requires precise project planning at an early stage, a competent project team, a sophisticated application system and a filing strategy which meets the time-to-market approach. The example below shows a freeze-dried dual-chamber system introduced in clinical phase III and transferred to a third-party manufacturer. The different planning steps and milestones with respect to key questions, conditions, results and further actions are discussed.

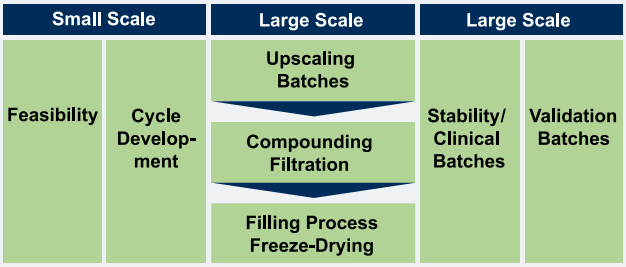
Project Planning

Precise planning is required for an upcoming transfer project to ensure the time-to-market concept for a new product. The project is split into several phases: project pre-phase, project start-up, development phase, validation and handover to commercial production. It is extremely important for both parties to establish competent project teams. The project managers coordinate the entire project and define work packages for the team members.



Development Phases

The project pre-phase involves reviewing the client's "Request for Proposal" and evaluating technical possibilities. The selected option is defined in detail during project start-up. The project is planned in relation to time, budget and quality. A project team is defined, work packages are addressed and the milestones of the project are set by both parties (third party manufacturer and client). During the development phase the primary packaging material is specified by the client and, if applicable, the dedicated equipment and the format and machine parts are evaluated between parties. The process development phase can be divided into:



Small scale

- Feasibility
- Cycle development

Large scale

- Upscaling batches
- Compounding/filtration
- Filling process/freeze-drying

Large scale

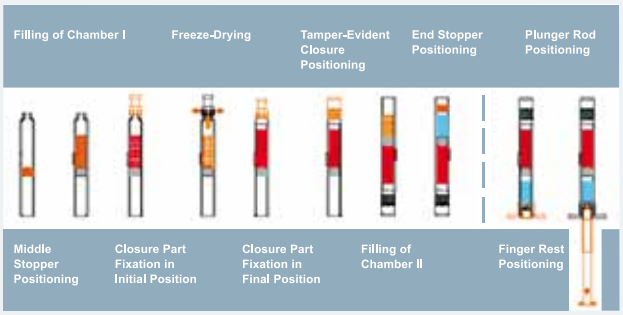
- Stability/clinical batches
- Validation batches

Basic conditions need to be defined between parties, key questions answered and further actions determined for all of the development phases described above.

Example

The described example of introducing a dual-chamber system for a freeze-dried application in clinical phase III requires all of the process development steps mentioned above. And although aseptic processing of a dual-chamber system is an established method, the process needs to be tailored to the needs of the API/formulation by the client.

The general filling process of chamber I, the freeze-drying process and the filling of chamber II are shown below.



The glass barrels are washed, siliconized and depyrogenated in a dry-heat tunnel. The middle stoppers are positioned after the barrels enter the filling suite. After the solution has been filled from above, the closure part is fixed in an initial position. The filled units are transported to the freeze-dryer and loaded. After freeze-drying the closure part is closed in its final position in the freeze-dryer and unloading and transport to the filling line for chamber II starts. Tamper-evident closures are mounted, the barrel is turned and the diluent is filled into chamber II from the back.

Development Phases

Feasibility

Formulation candidates and the target profile of the application (single-dose syringe, multi-dose cartridge) need to be selected between the parties for initial feasibility studies. An efficient lyo-cycle is developed on the basis of a package of physical/chemical data (tg, tg'). Definition of the sensitive APIs is important during this phase. A protocol and a report are issued for each freeze-drying run (including the preparation steps). The initial feasibility studies yield samples to examine moisture content, reconstitution behavior, chemical stability, turbidity, appearance, mechanical stability of the cake, and functionality of application.

Cycle Development

One or two promising formulation candidates are chosen by the parties based on the results of the feasibility study. The freeze-drying cycle is developed during several runs. The large-scale conditions employed down the road should be simulated during this stage. Each run is documented in a protocol/report. The samples of the different runs are subjected to informal stability testing, usually at 2-8°C, RT, 40°C / 75% relative humidity. The best cycle and formulation are selected after approximately three months.

Preparations for Upscaling

Preparations for upscaling (to production equipment) can begin while informal stability testing is under way. The equipment is considered, suppliers of raw materials and packaging materials are evaluated, and API-specific method transfers and microbiological qualification of the packaging materials are assessed.

Upscaling

Upscaling comprises the detailed evaluation of the different process steps employed during commercial manufacturing. The filtration setup is specified. The filling profile and the freeze-drying cycle are tested by performing various runs at minimum and maximum scale including extensive moisture mapping to verify homogeneity throughout the batch. Upscaling batches are produced on production-scale equipment (using the planned commercial setup). Thermocouples are placed inside the product to compare the applied parameters to the lab scale. These batches are therefore not for human use but produced according to GMP. The samples can be used for informal stability studies.

Stability/Clinical Batches

Clinical batches can be produced when the upscaling batches have been confirmed as successful. The basic conditions are GMP, human use, batch release by QC/QA, validated equipment and methods.

Cycle Robustness

Cycle robustness serves to challenge the limits of the process and is performed on production scale equipment. It could be of interest to place those not for human use batches on stability to judge later on deviations in commercial production. If cycle robustness was performed the validation batches are produced on target.

Validation

Before the validation campaign can commence, a detailed risk analysis of all process steps involved needs to be performed. All identified critical parameters such as holding times, mixing properties, full-day production are part of the validation study. One approach involves simulating the process parameters, worst-case conditions and validating optional minimum and maximum batch sizes for flexibility in commercial production. Parallel to the validation of the aseptic process, the shipping configuration should be validated. The validation batches constitute full-scale production material for the client. They are used in part for stability studies. These batches can also be used for the market launch, provided that they have sufficient shelf life. The documentation consists of a validation protocol and report including the conclusions for further commercial batches. The validation summary (and/or report) is provided to the authorities with the submission file.

Handover to Production

The official handover to production takes place in the form of the first three commercial batches. The project team prepares all relevant documents and executes a formal handover by training the production personnel, explaining the process steps and providing a summary of development activities, specialties and conclusions. The handover constitutes the official completion of the development project.

Conclusion

Precise planning of an upcoming project is a must to meet the time-to-market approach. The goal is to establish a competent project team and to structure the project according to the needs of development. At an early stage, the critical path needs to be identified and considered. The filing strategy including the development package needs to be discussed with the agencies at an early stage.

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