Guidance for Technology Transfer

This document provides comprehensive guidance on technology transfer processes in the pharmaceutical industry. It covers all aspects of transferring product and process knowledge between development and manufacturing sites to achieve successful product realization. The guidelines address evaluation, planning, preparation, execution, assessment, and post-transfer phases of technology transfer for both new products and site transfers.

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Introduction and Background

Technology transfer is a critical process in the pharmaceutical industry for transferring product and process knowledge between development and manufacturing sites. The goal is to transfer this knowledge to achieve product realization while ensuring product quality and patient safety. This guidance document outlines best practices for conducting effective technology transfers, covering all phases from initial evaluation to post-transfer activities.

Key aspects addressed include:

- Defining technology transfer and its importance
- Outlining responsibilities of sending and receiving units
- Providing a framework for planning and executing transfers
- Emphasizing quality risk management principles
- Aligning with regulatory expectations and GMP requirements

Scope and Purpose

This guidance document is applicable to:

- All technology transfers from R&D to manufacturing plants
- Transfers from exhibit scale to validation batches
- Transfers between manufacturing sites (own sites or contract manufacturing sites)
- Manufacturing processes and analytical methods transferred between sending and receiving units

The purpose is to define procedures for effective technology transfer in order to:

- Ensure consistent product quality and performance
- Minimize risks during transfer activities
- Provide a framework for planning and executing transfers
- Align with regulatory requirements and expectations

Key Definitions

Important terms defined in the guidance document include:

- Technology Transfer: The process of sharing skills, knowledge, technologies, methods of manufacturing, and facilities between organizations
- Sending Unit (SU): The organization from where a product, process or method is transferred
- Receiving Unit (RU): The organization where a product, process or method is received
- Critical Quality Attributes (CQAs): Physical, chemical, biological, or microbiological properties that should be within appropriate limits to ensure desired product quality
- Critical Process Parameters (CPPs): Process parameters whose variability has an impact on a CQA and therefore should be monitored or controlled

Responsibilities in Technology Transfer

For New Products (From R&D to Plant)

1 Formulation Development Department (FDD)

Share Master Formula Card and other details as per Annexure 1 & 2 with the plant team

2 Analytical Development Department (ADD)

Share materials, reagents, product specifications, protocols, and other details required for Analytical Method Transfer as per Annexure-1

3 Packaging Development Department (PDD)

Share Master Packaging Card and other details related to packaging process as per Annexure-1

4 Manufacturing Science & Technology (MS&T)

Review documents provided by R&D, prepare documents for Scale Up/Exhibit batches, coordinate with cross-functional teams for smooth transfer of technology

Responsibilities in Technology Transfer (Continued)

1 **Manufacturing**

Review Scale Up/Exhibit batch documents and support manufacturing of batches

2 **Quality Assurance**

Review/authorize all documents, prepare protocols and conduct studies as per requirement

3 **Quality Control**

Perform analytical method transfer and sample analysis of Scale Up/Exhibit batches

4 **Regulatory Affairs**

Review data/documents and support regulatory filing

For Site Transfer Products

1 **Manufacturing Science & Technology (MS&T)**

Review Sending Site documents, absorb technology, scale up at plant with support from cross-functional teams, execute characterization/feasibility/exhibit/pre-validation/process validation studies

2 **Plant Head (Sending Unit)**

Provide site transfer dossier to proposed manufacturing locations

Responsibilities in Technology Transfer (Continued)

1

Plant Head (Receiving Unit)

Receive site transfer dossier, allocate for evaluation by respective functions, schedule manufacturing and packaging of batches

2

Planning/Project Management/Purchase

Procure and ensure availability of required raw materials/packaging materials for Scale-up/Exhibit/Process Validation Batches as per schedule

3

Regulatory Affairs

Ensure applicable license availability, regulatory filing of exhibit batches, evaluate site transfer products for manufacturing process, equipment details, batch size, change parts procurement

4

Manufacturing

Execute Scale-up and Exhibit Batches in collaboration with MS&T and documentation thereof

Responsibilities in Technology Transfer (Continued)

1

Quality Control

Ensure availability of approved specifications and analytical test procedures, ensure testing and release for scale up and exhibit batch execution, ensure availability of analytical method transfer activity, test scale up and exhibit batch samples

2

Quality Assurance

Review and approve technology transfer documents for accuracy, completeness and correct transcription of information, review and approve other documents/reports as needed

3

Engineering

Ensure availability of requisite utilities and equipment

Process Design and Technology Transfer Phases

The technology transfer process is divided into different phases:

1. **Evaluation and decision phase**

   Assess feasibility and make decision to proceed with transfer

2. **Planning phase**

   Develop detailed transfer plan and assemble team

3. **Preparation phase**

   Gather and share all relevant information between units

4. **Execution phase**

   Manufacture exhibit/validation batches at receiving unit

5. **Assessment phase**

   Evaluate results and address any issues

6. **Closure and Post-transfer phase**

   Finalize transfer and implement continuous verification

Quality by Design (QbD) Approach

The guidance emphasizes using a Quality by Design (QbD) approach during pharmaceutical product development to assist in technology transfer. Key elements of QbD include:

1. **QTPP (Quality Target Product Profile)**

   Defines the quality characteristics of the drug product that ideally will be achieved

2. **CQAs (Critical Quality Attributes)**

   Physical, chemical, biological, or microbiological properties that should be within appropriate limits to ensure product quality

3. **Risk Assessment**

   Identifying which material attributes and process parameters potentially affect product CQAs

4. **DOE (Design of Experiments)**

   Systematic approach to optimize drug products and processes

Quality by Design Approach (Continued)

1. **Design Space**

   Multidimensional combination of input variables and process parameters providing assurance of quality

2. **Control Strategy**

   Planned set of controls derived from product and process understanding to ensure consistent quality

3. **Lifecycle Management**

   Continual improvement throughout the product lifecycle

The guidance also outlines a similar QbD approach for Analytical Method Development, including:

1. **ATP (Analytical Target Profile)**

   Defines the goal of the analytical method development process

2. **MODR (Method Operable Design Region)**

   Multidimensional space based on method factors and settings that provide suitable method performance

Evaluation and Decision Phase

Key activities during the Evaluation and Decision Phase include:

- For new products, Development lab should develop the product considering QbD approach for formulation, analytical and process aspects
- Finalize submission batch size and equipment in consultation with Supply chain, Regulatory & site Manufacturing Science & Transfer group
- For commercial/legacy products, Supply chain to identify and initiate site shift activity based on plant capacity, business strategy, regulatory requirements
- Address legal and economic implications, including intellectual property rights, royalties, pricing, conflict of interest and confidentiality

Planning Phase

Key activities during the Planning Phase include:

- Nominate Technology transfer team members from various departments
- Team should include representatives from:
  - Manufacturing/Production
  - Logistics/Supply chain
  - Engineering
  - Manufacturing science and technology group
  - Quality unit (QC/QA)
  - Health, safety and environment
  - Regulatory affairs
  - Analytical method transfer team
  - Research scientists
- Assess Receiving Unit's ability to accommodate intended production capacity
- Determine if production will be single-batch, continuous, or campaign-based

Preparation Phase

Key activities during the Preparation Phase include:

- Development center to share all relevant information with receiving unit, including:
  - Critical Material Attributes (CMAs)
  - Critical Process Parameters (CPPs)
  - Critical Quality Attributes (CQAs)
  - Challenge study data
  - Impact assessments
  - Control strategies
  - Stability data
- Prepare equipment equivalency and scale-up correlation report
- Finalize Product Development Report (PDR), product specifications, and stability study proposal
- Evaluate applicable Process Analytical Technology (PAT) applications
- Conduct risk assessment with all cross-functional teams
- Establish risk mitigation plan and control strategy based on residual risks

Knowledge Sharing

The Preparation Phase includes comprehensive knowledge sharing between the Sending Unit and Receiving Unit. Key aspects include:

- Detailed product characterization (composition, physical description, manufacturing method)
- In-process controls and specifications
- Packaging components and configurations
- Safety and handling considerations
- Summary of knowledge gained from development batches
- Information on scale-up activities and optimization
- Critical process parameters and their impact on critical quality attributes
- Change history and reasons for any process modifications
- Information on investigations of problems and outcomes

The Quality Assurance department of the receiving unit should maintain records of knowledge sharing sessions, including presentations and minutes of meetings.

Technology Documents Transfer

Key documents to be transferred from the Sending Unit to the Receiving Unit include:

1. Information on starting materials, applicable MSDS and storage requirements
2. Formulation Process Evaluation
3. Raw Material/Packaging Material specifications and Standard Test Procedures
4. In-process, Intermediate, Semi-finished, Finished, and Shelf-life stage specifications
5. Description of analytical methods
6. Method Validation reports
7. Method of analysis for dissolution profile (where applicable)
8. Risk assessment forms
9. Identification and justification of control strategy
10. Master Formula Card and Master Packaging Document
11. Process Analytical Technology (PAT) related documents
12. Stability/Transit/In-Use/Freeze-thaw Stability Protocol information
13. In-process sampling protocols and Finished Product sampling protocols
14. Analytical Method Transfer Protocol, Data sheet, and report
15. Product Development Report (PDR) and Packaging Development Report

Analytical Method Transfer

Key considerations for analytical method transfer include:

- Implement analytical methods at the Receiving Unit before testing process validation samples
- Prepare a protocol defining steps for transferring analytical methods
- Protocol should include objective, scope, responsibilities, materials and methods, experimental design, acceptance criteria, documentation requirements, and reference samples

Responsibilities of the Sending Unit:

- Provide method-specific training
- Assist in analysis of QC testing results
- Define methods to be transferred and experimental design
- Provide validation reports and demonstrate method robustness
- Provide details of equipment used and standard reference samples
- Review and approve transfer reports

Responsibilities of the Receiving Unit:

- Review and agree on acceptance criteria before execution
- Ensure necessary equipment is available and qualified
- Ensure trained personnel are in place
- Execute the method transfer protocol
- Perform appropriate level of validation to support method implementation
- Generate and obtain approval of transfer reports

Execution Phase – Exhibit Batches

Key activities during the Execution Phase for exhibit batches include:

- Plan manufacturing of batch(es) after ensuring availability of required facilities, approved documents, raw materials, and manufacturing license
- Consider producing trial/demonstration batches to confirm process capability before formal validation
- Exemption of trial/engineering batches may be possible based on scientific justification (e.g., scale-up factor application)
- Execute exhibit cum process validation batches and cleaning validation once process capability is established
- Implement higher level of sampling, additional testing, and greater scrutiny of process performance compared to routine production
- Ensure level of monitoring and testing is sufficient to confirm uniform product quality throughout the batch
- Communicate any problems identified during transfer back to the Sending Unit
- Based on successful completion of exhibit batches, provide recommendations for process parameters to be added or updated for process validation batches

Assessment Phase

Key activities during the Assessment Phase include:

- Review and revise relevant documents based on outcomes of exhibit/submission batches
- Ensure process evaluation of submission batches is completed and concluded
- Subject batches to stability studies
- Prepare submission batch summary report, reviewed by Sending Unit and cross-functional team
- Address any residual risks and control strategies in batch summary report
- Initiate change control for any modifications suggested by regulatory agencies after filing
- Conduct risk assessment for any changes in documents

For validation cum commercial batches:

- Decide product launch based on regulatory approval and patent expiry timeline
- Determine batch size based on commercial volume, equipment capacities, and regulatory guidance
- Review and evaluate any specification changes resulting from regulatory queries
- Plan characterization/pre-validation batches to optimize process parameters if batch size or equipment changes
- Plan real hold time batches to justify proposed hold times in Batch Manufacturing Records

Hold Time Studies

Key considerations for hold time studies include:

- Perform risk assessment to determine requirements for hold time studies, testing time points, and testing requirements
- Conduct studies at various stages of product lifecycle (development, scale-up, validation, commercial)
- Real Hold Time Study: Subject entire batch to hold time at each stage before proceeding to next stage
- Use same raw materials, manufacturing process, and equivalent equipment as approved product
- Store batch in actual simulated conditions of quarantine/manufacturing areas
- Charge batches on accelerated and long-term stability conditions
- Release to market after satisfactory 3-month accelerated stability data, statistical evaluation, and regulatory acceptance

Process Validation Approaches

Two main approaches for process validation of new products:

1 Prospective Validation

Typically involves validation of three batches

2 Concurrent Validation

Used for certain categories of drugs (e.g., orphan drugs, low demand, short shelf life), involving validation of one batch at a time

Key steps in process validation:

1. Develop a Validation Master Plan (VMP)
2. Prepare a detailed validation protocol, including:
    - Protocol approval
    - Training records
    - General information and objectives
    - Background and pre-validation activities summary
    - Design and scope
    - List of equipment and their qualification status
    - Facilities qualification
    - Process flow chart
    - Risk assessment strategy and approach
    - Evaluation of formulation ingredients, raw materials, and equipment
    - Manufacturing procedure narrative
    - List of critical processing parameters and critical excipients
    - Sampling, tests, and specifications
    - Acceptance criteria
    - Deviation handling procedures

Packaging Validation

Key considerations for packaging validation:

- Perform packaging validation as critically as drug product process validation
- Recognize packaging as the interface between drug product and environment
- Conduct packaging process re-validation when there are changes in material source, packaging material, process, equipment, or support systems
- Perform risk assessment prior to packaging validation, considering equipment, process, parameters, and type of packaging
- Parameters may vary based on packaging type (e.g., HDPE bottle, blister packaging, Alu-Alu)

Stages of packaging validation:

1. Process Design: Includes feasibility studies, development of new packs, risk assessment, and process qualification
2. Pre-Stage 2: Verify packaging process parameters during exhibit/pre-validation batches
3. Process Qualification: Conduct packaging process verification during PPQ batches
4. Continued Process Verification: Monitor CPV parameters and conduct rejection trend analysis

Closure and Post-Transfer Phase

Criteria for successful technology transfer:

- Documented evidence that the Receiving Unit can routinely reproduce the transferred product, process, or method against predefined specifications
- Product quality meets pre-established criteria
- Process performance is as expected when compared with historical data
- Confirmation that the control strategy is executable and delivers product meeting CQAs and specifications
- Successful analytical method validation/verification
- Completion of any additional batches required as part of the closure assessment

Post-Transfer Phase (Continued Process Verification):

- Goal is continual assurance that the process remains in a state of control during commercial manufacture
- Implement system(s) for detecting unplanned departures from the process as designed
- Collect and evaluate information about process performance to detect undesired process variability
- Take action to correct, anticipate, and prevent problems to maintain process control

References and Guidelines

The guidance document references several important regulatory guidelines and industry best practices, including:

- International Council for Harmonisation (ICH) guidelines:
  - Q8(R2) Pharmaceutical Development
  - Q9 Quality Risk Management
  - Q10 Pharmaceutical Quality System
  - Q12 Life Cycle Management
  - Q14 Analytical Procedure Development
- Good Practice Guide: Technology Transfer
- WHO guidelines on the transfer of technology in pharmaceutical manufacturing
- USFDA Guidance for Industry Process Validation: General Principle and Practices
- European Medicine Agency: Guideline on Process validation for finished product
- ISPE guidance on packaging validation

Appendices Overview

The guidance document includes several appendices providing additional details and checklists:

1. Content of Knowledge Sharing
2. Exhibit Batch Initiation Checklist
3. Process Parameters to be Considered During Technology Transfer
4. Product Launch Checklist
5. Site Transfer Checklist
6. Process Parameters for Packaging Validation (Blister & Bottle Packaging)
7. Technology Transfer Dos and Don'ts
8. Training Needs for Technology Transfer

These appendices provide practical tools and detailed information to support the implementation of the technology transfer guidance.

Appendix I: Content of Knowledge Sharing

This appendix outlines the key information to be shared during technology transfer, including:

- API-related and general information:
  - Impact of API particle size on product performance
  - Effect of API quality attributes variation
  - API degradation studies
  - Effect of different API vendors
  - API physical properties data
- Formulation and process information:
  - Rationale for excipient selection
  - Innovator product details and comparison
  - Preformulation study data
  - DOE study data for process/formula optimization
  - CPP/CQA/CMA risk assessment and mitigation plan
- Unit operation-specific information (e.g., dry mixing, granulation, drying, tableting, coating)
- Analytical method information
- Packaging development information