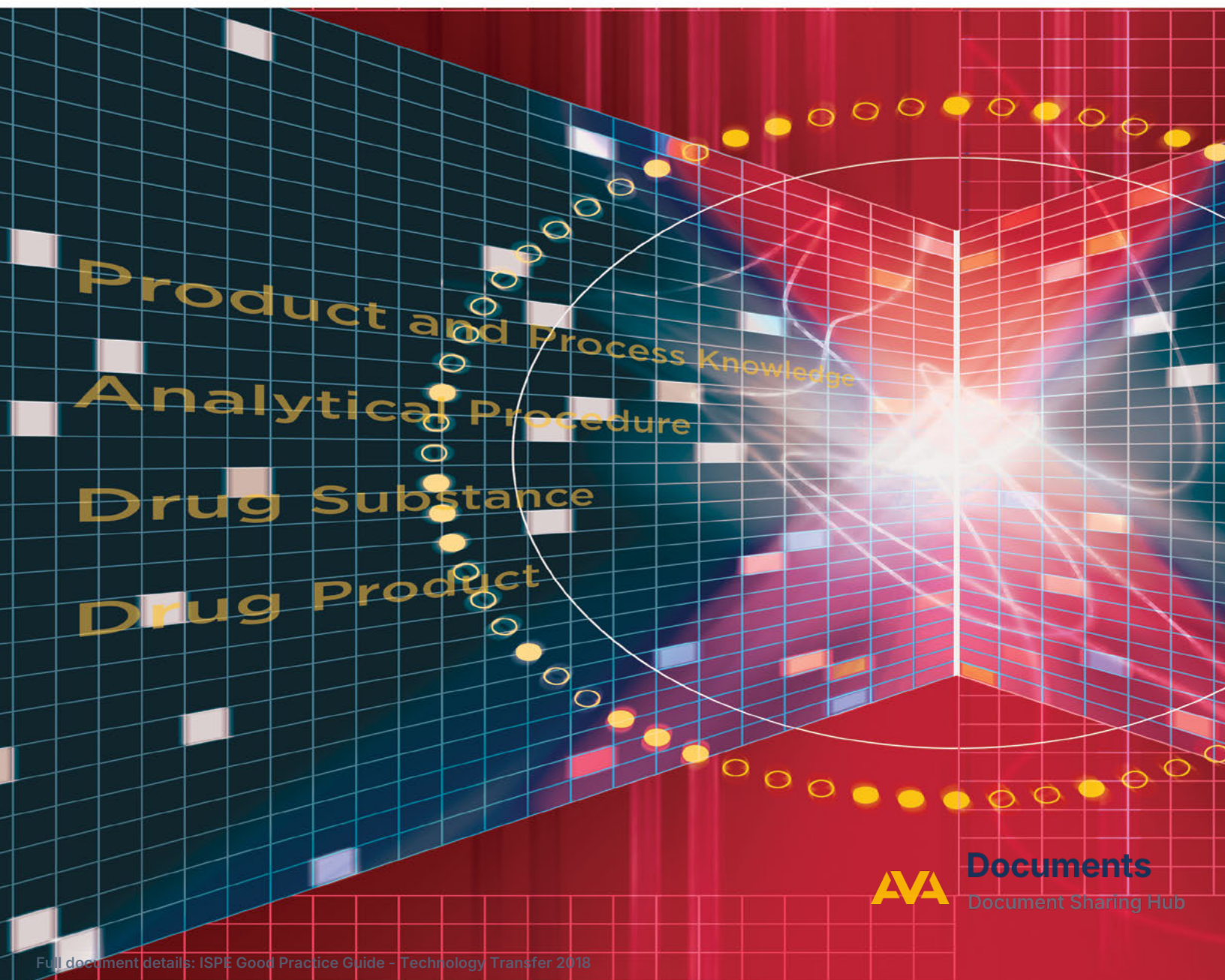


GOOD PRACTICE GUIDE:

Technology Transfer

Third Edition





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Technology Transfer

Third Edition

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Preface

Transfer of manufacturing processes and analytical procedures between facilities or laboratories is a necessary part of pharmaceutical development and commercialization. Technology transfers take the outputs of process or method development activities and transfer the knowledge to a different location where a process or analytical procedure will be operated. This third edition of the ISPE Good Practice Guide: Technology Transfer was developed by an international team of authors from across the industry. This Guide presents a general approach and good practices for effective technology transfer with redacted case studies as examples. The intent is for the reader to utilize Chapters 1, 2, and 3 as a foundation and the subsequent chapters as applicable. The reader is encouraged to utilize the various lists, tables, figures, and templates for illustrative purposes.

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1 Introduction

1.1 Background and Purpose

Transfer of manufacturing processes and analytical procedures between facilities or laboratories is a necessary part of pharmaceutical development and commercialization. Technology transfers may utilize the outputs of process and method development activities and/or documentation of established processes and methods. Knowledge of the product and the manufacturing process is the basis for transfer to a different location (which could be a different site, country, or facility on the same site) where a process or analytical procedure will be operated.

This Guide focuses on how technology transfer can be achieved.

Technology transfer is defined in ICH Q10 [1] paragraph 3.1.2 as follows:

“The goal of technology transfer activities is to transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realisation. This knowledge forms the basis for the manufacturing process, control strategy, process validation approach and ongoing continual improvement.”

Technology transfer projects may take place at various points during the product lifecycle. Successful transfers depend on robust project management processes combined with appropriate product and process understanding. They require partnership, cooperation, and coordination between the sending and receiving units to ensure successful and efficient completion, such that the receiving unit can manufacture, test, and release a safe, efficacious, and quality product comparable to that of the sending unit.

Technology transfer projects are dependent on the development and characterization of robust processes that allow consistent and predictable operation of these processes. Similarly, development of robust analytical methods enables timely transfer of methods. These are particularly important aspects; if processes are not well developed and sources of variation are not well known, e.g., due to incomplete or inadequate process/product knowledge, then technology transfer will not be robust.

This Guide has been designed to present industry good practices for successful and efficient execution of technology transfer projects and to achieve a balance between risk management and cost effectiveness while aligning with applicable regulatory expectations, as described in ICH Q7, Q8(R2), Q9, Q10, and Q11 [2, 3, 4, 1, 5] and other regulatory documents. It covers the principles of technology transfer and provides tools for its practical application.

The impetus for technology transfer varies and may be based on several factors, for example:

Progression in a product development lifecycle, from development through scale-up to commercialization
The need for additional manufacturing capacity driven by increased demand or risk mitigation

- The need to streamline capacity when volumes fall, e.g., at patent expiry, when products change commercial status from novel to generic, etc.
- Strategic requirements to relocate business units, e.g., regional economic advantages, regional requirements for local manufacture, global expansion in different regions of the world, etc.
- Identification and qualification of local analytical facilities for testing of intermediates and finished products to meet regional regulatory requirements
- Dual sourcing strategies to mitigate demand variability or to reduce sourcing risks from manufacturing sites

- Ensuring adequate turnaround times for analytical laboratories
- Utilization of virtual organizational structures and increasing use of third parties

1.2 Rationale for this Third Edition

The Guide has been updated to ensure alignment with relevant guidance publications and terminology used by industry and regulators. Practical case study examples have been added to this third edition; see Chapter 9 (Appendix 2) and Chapter 10 (Appendix 3).

This third edition of this Guide highlights the following:

- Alignment with science and risk-based (Quality by Design (QbD)) principles described in ICH Q8(R2) Pharmaceutical Development [3], ICH Q9 Quality Risk Management [4], ICH Q10 Pharmaceutical Quality System [1], and ICH Q11 Development and Manufacture of Drug Substance [5], including reference to Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs), material attributes, design space (where used) and, in particular, control strategy
- Alignment with the process validation concepts and lifecycle approach as described in:
 - ICH Q10 and Q11 [1, 5]
 - FDA Guidance for Industry – Process Validation: General Principles and Practices (January 2011) [6]
 - EMA Guideline on process validation for finished products – information and data to be provided in regulatory submissions (November 2016) [7]
 - EU GMP Annex 15 Qualification & Validation [8] and similar PIC/S [9] guidances
 - EMA Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission (April 2016) [10]
- Recognition that knowledge management is a critical component of effective technology transfer and that companies have employed various practices and technologies to identify and manage knowledge throughout the development and manufacturing lifecycle including technology transfer.
 - Knowledge includes product and process understanding and the science and risk-based approaches to gaining such understanding. Refer to the *ISPE Guide Series: Product Quality Lifecycle Implementation (PQLI®) from Concept to Continual Improvement* [11] for examples of practical application of science and risk-based approaches. See also the *ISPE Concept Paper: Implementing Knowledge Management in Bioprocess* [12].
 - Knowledge management also includes assessing what data will be collected to support a control strategy, how this will be managed, and identifying Key Performance Indicators (KPIs). These activities ensure that the full product lifecycle (from initial development to product discontinuation) and all elements of the technology transfer are optimized to avoid, for example, irrelevant data collection/analysis or making comparisons between the style or approach of the sending and receiving units.
 - Examples of knowledge to be transferred include:
 - > Scientific and operational information
 - > Product quality attributes (e.g., CQAs and material attributes)

- > Overview of process, including unit operations (e.g., reference to Process Flow Diagrams, CPPs, material attributes, etc.)
- > Control strategy
- > Continuous/continual improvement ideas and plans
- > Tacit knowledge (i.e., knowledge from experience rather than explicit knowledge) and means to communicate this knowledge
- > Health, Safety, and Environment (HSE) requirements
- > Learning points from previous collaborative activities
- > Implications for use of specialist tools and techniques such as Process Analytical Technology (PAT), multivariate data analysis, calibration of models, advanced data analytics, etc.
- > Current understanding of potential risks to product quality
- Industry developments and potential regulatory impacts:
 - Technology transfers driven by acquisitions
 - Global expansion to developing countries
 - Facility consolidation within a company
 - Clinical to commercial transition within the same or different facilities
 - Supply chain driven events (e.g., economic drivers)
 - Utilization of Contract Manufacturing Organizations (CMOs) and contract development organizations, including virtual organizations
 - Increased utilization of platform and single-use systems
 - Introduction of generics and biosimilars
 - Cost efficiencies, either capital or revenue driven
 - Reduced cycle times
 - Local regulatory requirements (e.g., which may influence need to manufacture locally)
- Recognition that having a robust quality culture, for both sending and receiving units, is important for ensuring successful technology transfer. This is particularly important where cultures are very different between sending and receiving units, which may be due to internal organizational structures, management styles, country specifics, or just individual approaches; these differences should be recognized early and steps taken to ensure appropriate understanding and alignment during the technology transfer. Refer to the *ISPE Cultural Excellence Report* (April 2017) [13] for additional information on this topic.

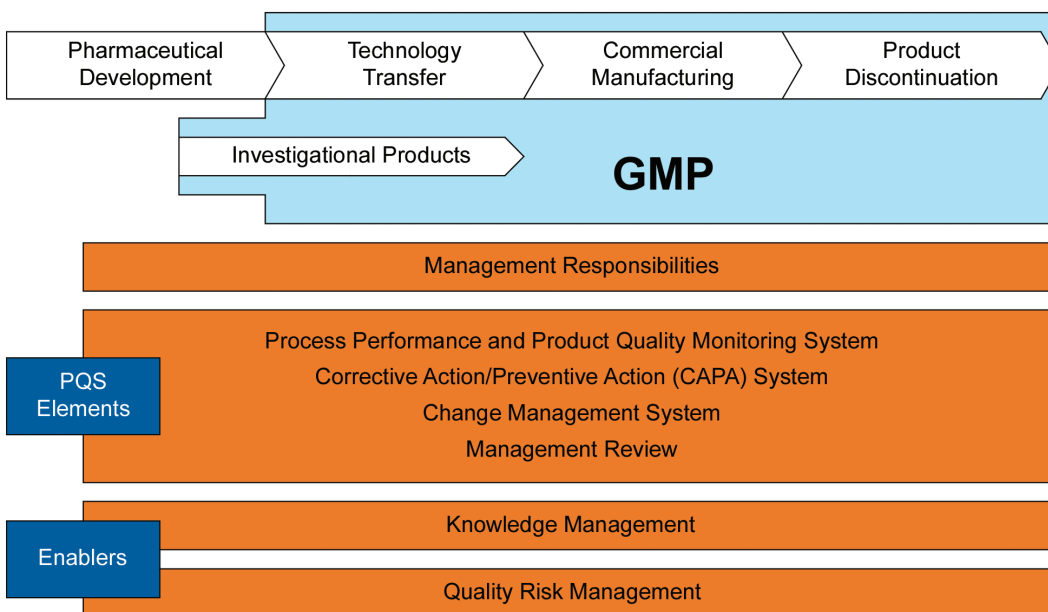
Helpful guidance is also given in the WHO Technical Report No. 961, Annex 7, WHO guidelines on transfer of technology in pharmaceutical manufacturing [14] and the Japan National Institute of Health Sciences, Guideline for Technology Transfer (Draft) [15]. The FDA Guidance for Industry – Contract Manufacturing Arrangements for Drug Quality Agreement, November 2016 [16] also mentions transfers.

1.2.1 ICH Q10 Pharmaceutical Quality System [1] and Technology Transfer

ICH Q10 [1] illustrates the Pharmaceutical Quality System (PQS), as shown in Figure 1.1, and states:

“The PQS covers the entire lifecycle of a product including pharmaceutical development, technology transfer, commercial manufacturing, and product discontinuation as illustrated by the upper portion of the diagram.”

Figure 1.1: Diagram from ICH Q10 Pharmaceutical Quality System [1]



ICH Q10 [1] also covers the following topics and states the following about them in relation to technology transfer:

- **Product Lifecycle**

The product lifecycle, in relation to technology transfers, includes the following activities:

- “New product transfers during Development through Manufacturing”
- “Transfers within or between manufacturing and testing sites for marketed products”

- **Knowledge Management**

“Product and process knowledge should be managed from development through the commercial life of the product up to and including product discontinuation. For example, development activities using scientific approaches provide knowledge for product and process understanding. Knowledge management is a systematic approach to acquiring, analysing, storing and disseminating information related to products, manufacturing processes and components. Sources of knowledge include, but are not limited to prior knowledge (public domain or internally documented); pharmaceutical development studies; technology transfer activities; process validation studies over the product lifecycle; manufacturing experience; innovation; continual improvement; and change management activities.”

- **Management of Change in Product Ownership**

"When product ownership changes, (e.g., through acquisitions) management should consider the complexity of this and ensure:

(a) The ongoing responsibilities are defined for each company involved;

(b) The necessary information is transferred."

- **Application of Process Performance and Product Quality Monitoring System throughout the Product Lifecycle**

"Monitoring during scale-up activities can provide a preliminary indication of process performance and the successful integration into manufacturing. Knowledge obtained during transfer and scale up activities can be useful in further developing the control strategy."

- **Application of Corrective Action and Preventive Action (CAPA) System throughout the Product Lifecycle**

"CAPA can be used as an effective system for feedback, feedforward and continual improvement."

- **Application of Change Management System throughout the Product Lifecycle**

"The change management system should provide management and documentation of adjustments made to the process during technology transfer activities."

- **Application of Management Review of Process Performance and Product Quality throughout the Product Lifecycle**

"Aspects of management review should be performed to ensure the developed product and process can be manufactured at commercial scale."

1.2.2 Product Lifecycle

Technology transfer expectations are different during the various phases of the product lifecycle. This Guide addresses the transfer of technology from a sending unit to a receiving unit, which may occur at any time during the lifecycle. To be a manageable and useful tool, this Guide assumes all work performed prior to initiating a transfer phase is adequate for enabling transfer of drug substance and/or drug product processes and analytical methods during the product lifecycle.

Reference to the three stages of the process validation lifecycle described in FDA Guidance for Industry – Process Validation: General Principles and Practices [6] is helpful, particularly Stage 1 (Process Design) which relates to product and process understanding.

The adequacy of product and process understanding is fundamental to successful technology transfer. It starts in design and development and captures knowledge in a development report (e.g., includes initial document review, summaries of experiments, QTPP, CQAs, material attributes, identification of sources of variation, and potential risks to product quality, etc.). For generics, historical data on product and process understanding should be documented based on current knowledge.

Typically, limited development occurs during the technology transfer phase. Exceptions during transfers can be handled by using risk-based approaches when, for example:

- There are incomplete characterization or process development
- Scale-up is needed

- It is decided to start transfer very early (e.g., due to differing production and development site locations) and to make feasibility batches and carry out development work

Utilization of stage gates is an effective approach to initiating and managing a transfer when development and/or characterization activities are occurring in parallel to the transfer. See Chapters 2 and 3 for details of the phases. Refer to *ISPE Good Practice Guide: Project Management for the Pharmaceutical Industry* [17] for additional information on project management activities.

Investment in experience in the sending unit with the elements of the process or method being transferred can be used to accelerate transfers and close gaps in the technology transfer package. Examples include:

- **Solvent runs:** Running the process or selected operations of the process with process solvents only. This technique is useful to complete definition and test the effectiveness of site specific requirements in procedures, automation, and sampling strategies.
- **Live cell runs (in biological processes):** Can elucidate site specific sensitivities to process equipment and utilities by executing cell culture stages and monitoring performance. The cell culture phases are typically prioritized based on risk assessments which are informed by characterization data.
- **Simulation activities:** Can be used to complete the transfer package and test effectiveness without requiring either plant or laboratory time. These are often termed table tops, make-a-batch, simulation runs, virtual batch, or test-a-batch.
- **Engineering runs:** Executed prior to the initiation of process validation and typically without full GMP controls. Engineering runs (sometimes called dry runs) are valuable to obtain experience with processes which have significant differences from the sending unit knowledge base, e.g. changes in scale and equipment. In addition, they are useful for generating quantities of new sample types in support of enhanced control strategies. In some instances, they may be carried out after validation of the manufacturing process to characterize changes before making the choice of requalifying or revalidating equipment/processes (e.g., change of drug substance source).

The level of detail and depth of product and process knowledge (which generally will increase over time) should be adequate for the point in the lifecycle at which the transfer is taking place.

1.2.3 Intellectual Property and Confidentiality Agreements

Sending and receiving units would normally agree at an early stage what intellectual property can be shared between them or with third parties. From a commercial viewpoint, this is an important fundamental agreement that needs to be implemented early on before a transfer can be organized or its scope quantified. Intellectual property agreements and related confidentiality agreements are typically company and product specific.

1.2.4 Quality Agreements

A quality agreement is required when using a contract partner. It should be a separate document and includes the following aspects:

- Data integrity
- Data management and responsibility
- Information technology requirements
- Continued Process Verification and its reporting
- Any continual improvement initiatives

Refer to FDA Guidance for Industry – Contract Manufacturing Arrangements for Drugs: Quality Agreement [16], in which a quality agreement is defined as follows:

“A quality agreement is a comprehensive written agreement between parties involved in the contract manufacturing of drugs that defines and establishes each party’s manufacturing activities in terms of how each will comply with CGMP.”

The FDA guidance [16] states that quality agreements should cover manufacturing activities and change control associated with these activities. Manufacturing activities include quality unit activities, facilities and equipment, materials management, product specific considerations, laboratory controls, and documentation.

1.2.5 Science and Risk-Based Approaches and Control Strategy

Technology transfer can be considered to have these main components:

- Business strategy
- Regulatory strategy
- Understanding and agreement of the knowledge to be transferred
- Understanding of the control strategy to be transferred
- Robust project management (including accounting for differences in culture and styles of working)

Using science and risk-based (or QbD) approaches enable understanding about a product and its process and the link to patient requirements, and hence enable effective technology transfer. For legacy products, historical information should be captured and documented, including, for example, agreed acceptance criteria and ranges within which product quality has been achieved and a qualitative assessment of product attributes, etc.

Technology transfer should ensure knowledge of product, process, and operational aspects are transferred effectively between sending and receiving units and that risks and mitigation plans during each of the phases are understood.

QTPP, CQAs, CPPs, material attributes, and control strategy, as described in ICH Q8(R2) [3], are elements to product and process understanding and should be available during technology transfer. For drug substance, refer to ICH Q7 [2] and ICH Q11 [5].

Close partnership between Research and Development (R&D), global manufacturing, quality, regulatory, and commercial functions is required to define, develop, and commercialize a drug, and therefore, enable successful technology transfer. Deliverables from early development should include initial assessment of unit operations at commercial scale, CQAs, CPPs, material attributes, and control strategy.

Implementation of a robust control strategy is fundamental to a successful technology transfer. Establishing a robust control strategy requires a properly developed risk assessment (both for development and production), which depends on having adequate knowledge of the sources of variation.

As noted in Section 3.2.2, it is not the role of the technology to develop the control strategy. However, it is the responsibility of the technology transfer team to ensure the control strategy is effectively implemented; this will require specific inputs from the receiving unit (e.g., automation, alarm strategies, and process monitoring and sampling requirements).

An effective control strategy includes:

- Understanding the relationship between CQAs, CPPs, material attributes, and in-process controls

- Controls on material attributes (including raw materials, starting materials, intermediates, reagents, primary packaging materials for the drug substance, etc.)
- Controls implicit in the design of the manufacturing process (e.g., sequence of purification steps (for biotechnological/biological drug substances) or order of addition of reagents (for chemical entities))
- In-process controls (including in-process tests and control of process parameters)
- Controls on drug substance
- Understanding of analytical methods
- Having appropriate data
- Alarm strategies
- Completed and qualified engineering modifications for equipment or utilities
- Where applicable, PAT systems, closed loop controls, and validated PAT methods and models

Implementation of a control strategy also depends on having other requirements in place, e.g., GMP controls, stability and release testing, ensuring requirements for drug substance, drug product and primary/secondary packaging are in place, etc. This is sometimes referred to as an integrated control strategy or holistic manufacturing control strategy. There should also be a means to capture and manage learnings for continual improvement, e.g., from deviations. It is important that the receiving unit has as much information as possible to understand why certain requirements are needed, as this helps minimize potential future errors.

Undertaking small scale batch observation runs can offer the following benefits (particularly when a CMO is being used for pilot and production manufacturing):

- Helps to get support and agreement from production teams
- Improve knowledge of the process, reduce errors, and build bill of materials lists
- Allows for the receiving unit team to view these at the sending unit's site and, for example, to make video recordings as appropriate
 - Gives the receiving unit team a chance to obtain an understanding of the documentation they may receive

It can also include table top production batch walk throughs, using laboratory equipment, and models or drawings to mimic production and help build a scope of work.

Technology transfer processes should enable the transfer of the knowledge to assure that all controls are in place, for all stages of a product lifecycle.

Ensuring operators understand what has to be implemented is important; some companies include a qualification and training program as part of operator training. Training procedures can include a review of the process/product understanding and reading Standard Operating Procedures (SOPs), batch record, and protocols to ensure the process knowledge is understood. Technical groups should explain to operators why the CPPs and controls have specific ranges and, in particular, those which will have a negative impact if out of range.

1.2.6 **Quality Risk Management**

Quality Risk Management (QRM), as described in ICH Q9 [4], is an extremely important part of a technology transfer project. Successful technology transfer should ensure all high risk areas have been considered, appropriate mitigation has been put in place, and that any residual risks are assessed and agreed as acceptable between sites. The QRM process should be documented.

The sending and receiving units should follow QRM principles. SOPs related to QRM should be in place and followed in all aspects related to technology transfer.

The terminology, tools, and techniques from ICH Q9 [4] should be used appropriately. Refer to Section 3.3 for additional information. Refer to Chapter 12 (Appendix 5) and Chapter 13 (Appendix 6) for examples of Failure Mode and Effects Analysis (FMEA) and fishbone diagrams, respectively.

Risk assessments should ideally be carried out jointly by the sending and receiving units. There should be clear understanding of the purpose of each risk assessment. Any mitigations should be built into control strategies or other procedures at the receiving unit.

1.2.7 **Communication**

The success of technology transfer is critically dependent on good communication and relationships between personnel in technology transfer teams. At the start of a technology transfer, roles and responsibilities should be defined for transfer team members (from both sending and receiving units) including who are responsible and accountable for the components of the transfer.

Sending and receiving units should have the same level of understanding for all aspects of the transfer.

In addition, communication channels and methods (e.g., reports) that may affect the transfer of information should be defined. It is essential that good verbal and written communication channels are put in place, particularly when personnel are often not in the same room and therefore are unable to have face-to-face discussions, e.g., use of teleconferencing and video conferencing. The need to build good relationships and trust between the sending and receiving units is of great importance; capturing and documenting all appropriate knowledge is crucial so that it can be easily communicated between the sending and receiving units.

For transfers between companies, communication should be formalized by leveraging documents such as quality and supply agreements. A similar formality in principle should be put in place for intra-company transfers.

1.3 **Scope**

This Guide is intended to be used as a generic guide to technology transfer and compiles information under three main topics:

- Technology transfer of analytical methods
- Technology transfer of drug substance (active pharmaceutical ingredients (APIs))
- Technology transfer of drug product (dosage forms manufacturing processes)

Each topic should be read in conjunction with Chapters 2 and 3 of this Guide.

It is recognized that transfers of analytical methods, drug substance, and drug product are closely linked. Drug substance/drug product transfers cannot usually be performed correctly if the corresponding analytical methods are not transferred to validate the transfer for quality.

This Guide is intended to provide information for technology transfers between two parties (a sending unit and a receiving unit) for any applicable transfers in the product lifecycle, e.g.:

- Laboratory to laboratory scale
- Laboratory to development/pilot scale
- Development to clinical manufacturing
- Development to launch/commercial manufacturing
- Commercial to commercial manufacturing
- Drug substance to drug product manufacture
- Lead manufacturer to third party manufacturer

The sending and receiving units may be internal (within the same company) or external (between companies or to a third party such as a CMO). The transfer is normally from a sending unit that possesses the process knowledge, history, and operational experience to a receiving unit which needs to acquire that knowledge and leverage available experience to manufacture the drug.

Not all activities described in this Guide will apply to every transfer. Companies may select activities appropriate to the type and scale of technology transfer being performed.

This Guide does not intend to be a standard operating procedure for technology transfer. It reflects the understanding of industry as of the publication date.

This Guide is interpretive and ISPE cannot guarantee that a transfer performed in accordance with the recommendations in this Guide will be acceptable to regulatory authorities.

This Guide makes reference to, but does not cover, the following aspects:

- Regulatory guidance
- Qualification and process validation
- Product and process development

As further described in Chapter 3, for the purpose of this Guide, a technology transfer is considered complete after the close-out phase. Therefore, the topics of Continued Process Verification (CPV) and Continued Quality Verification (CQV) are beyond the scope of this Guide. Refer to ICH Q8(R2) [3], FDA Guidance for Industry – Process Validation: General Principles and Practices [6], and ASTM (American Society for Testing and Materials) E2537-16 Standard Guide for Application of Continuous Process Verification to Pharmaceutical and Biopharmaceutical Manufacturing [18] for guidance on CPV and CQV.

However, process validation is an important step to ensure technology transfer has been completed and the links are summarized in Table 1.1 in simple terms.

Table 1.1: Technology Transfer Links to Process Validation

Process Validation Stages [6]	Nomenclature (US)	Technology Transfer Links to Process Validation
1	Process Design	Technology transfer requires an understanding of what has to be transferred, e.g., CQAs, CPPs, material attributes, and control strategy.
2.1	Qualification of Utilities and Equipment	Utilities and equipment at the receiving unit (especially if it is different between sending and receiving units) is confirmed to operate over the ranges for the CPPs required.
2.2	Process Performance Qualification (PPQ)	Confirms the receiving unit can deliver the CQAs.
3	Continued Process Verification (CPV)	Ensures the receiving unit puts in place monitoring to ensure technology transfer has been successfully delivered.

1.4 Key Terms

This section introduces key terms as they are used in the context of this Guide. Refer to Chapter 15 for an expanded listing of definitions.

Control Strategy

As defined in ICH Q10 [1]:

“A planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.”

Receiving Unit

An organization, which includes core and auxiliary functions, where a designated product, process, or method is expected to be transferred to.

Core functions normally include quality, manufacturing, and process engineering. Auxiliary functions may include regulatory, supply chain, warehousing, and HSE. The actual balance of functions would be project specific.

Process Validation

- As defined in FDA Guidance for Industry – Process Validation: General Principles and Practices [6]:

“Collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product”

Note: This is a lifecycle definition covering the three stages as described by FDA.

- As defined in EMA Guideline on process validation for finished products – information and data to be provided in regulatory submissions [7]:

“Documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes”

Note: This definition refers to a single stage – equivalent to Stage 2.2 of FDA Guidance [6])

Quality Target Product Profile (QTPP)

As defined in ICH Q8(R2) [3]:

“A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.”

Sending Unit

An organization, which includes core and auxiliary functions, where a designated product, process, or method is expected to be transferred from.

Core functions normally include quality, manufacturing, and process engineering. Auxiliary functions may include regulatory, supply chain, warehousing, and HSE. The actual balance of functions would be project specific.

Stakeholder

Any individual, group, or organization that can affect, be affected by, or perceive itself to be affected by a transfer. Decision makers might also be stakeholders.

Technology Transfer Charter

The technology transfer charter captures the strategic intent and defines the overall scope of the technology transfer project. It should document the team members and their roles and responsibilities, explain the effort and time required for the technology transfer project, and identify significant assumptions and risks. The charter helps to ensure that management and team members from both sending and receiving units understand the project and agree upon deliverables.

Note: The technology transfer charter and proposal may be the same document, depending on the complexity of the technology transfer project. If the charter elements change, the project needs to be reevaluated, no matter what stage it is at in the technology transfer.

Technology Transfer Proposal

The technology transfer proposal defines the overall scope of the project, documents the team members and their roles and responsibilities, estimates the effort and time required for the project, establishes high level success criteria, and identifies significant assumptions and risks. This document is intended to ensure that stakeholders and team members from both sending and receiving units understand the project and agree upon the deliverables. The technology transfer proposal also identifies information needed for the technology transfer package. The technology transfer proposal should be reviewed and approved by the appropriate stakeholders from both sending units and receiving units. The proposal may be managed using formal change control procedures.

Note: The technology transfer charter and proposal may be the same document, depending on the complexity of the technology transfer project.

Technology Transfer Plan

The technology transfer plan is based on the technology transfer proposal. It provides a more detailed description of the elements of the project (both technical and project management) that are to be completed by the team to achieve the overall goals. The technology transfer plan provides a means of ensuring alignment of the team members around the specific activities, as well as a means of tracking progress of the project. Results from risk identification/gap analysis, risk assessment, and mitigation planning should be included. Any mitigation actions identified as part of the gap/risk assessment and expected deliverables should be included in the plan. Timeline, resources and budget, assumptions, regulatory strategy, and success criteria should be updated, as required. Major technology transfer execution activities should be listed. The plan should be managed using formal change control procedures, e.g., the receiving unit should follow their own change management system and related SOPs.

Technology Transfer Protocol

The technology transfer protocol is sometimes built into the proposal but may be a separate document. It defines the specific elements of the transfer activities, acceptance criteria (especially for analytical method transfers), and success criteria.

Technology Transfer Package

The technology transfer package is the collection of all (including local and process related) knowledge required to run the process and analyze the product. Depending on the stage of the product lifecycle, this may include, for example:

- Process definition documents containing tables of operating parameters and process development reports, e.g., for an early stage clinical process
- License requirements
- Validation studies
- Historical in-process data (can be information from many sources including annual product reviews and product quality reviews)
- Analytical method development history, including sample libraries
- Tacit knowledge and process experience, i.e., practical information that may or may not be initially documented

The technology transfer team should identify information (e.g., from product, process, equipment, raw materials facilities and suppliers) that needs to be collated, along with associated responsibilities, to help to ensure an effective knowledge transfer. A list of deliverables per discipline, including whether the sending or receiving unit is responsible, should be developed and formalized at the peer to peer meetings. This information gives direction and goals to both units, establishes who is the owner of the product lifecycle file, and ensures alignment of both units to an agreed plan (see Chapter 3).

2 Technology Transfer – Planning Considerations and Success Criteria

2.1 Introduction

This chapter provides guidance on what to consider for a transfer, including establishing success criteria, prior to the formal formation of the full technology transfer team. Guidance provided is applicable to drug substance, drug product, and analytical procedure technology transfers.

A technology transfer typically starts with an agreement (referred to as a charter in Chapter 3) normally formalized or on a contractual basis between a sending unit and a receiving unit for the transfer of, e.g., a developed process or a commercial process or an analytical method.

The success of a technology transfer project will be largely dependent upon the skill and performance of individuals assigned to the project from both the sending unit and the receiving unit. It is, therefore, critical that a clear objective for any technology transfer project be developed. It is also critical that a project team comprised of individuals from both the sending unit and the receiving unit is established and that there is a precise understanding of each team member's role and responsibility prior to initiation of the technology transfer project.

Skill alone will not ensure a successful technology transfer project. Once a project has been identified and a team chosen, a clear and realistic project implementation plan is required to guide the project, manage expectations, and handle the inevitable deviations and changes that may present themselves during implementation.

Along with that plan comes the need to consider the relationship between the various tasks associated with a successful technology transfer. It should be clearly understood that each technology transfer assignment is unique; therefore, it is impossible to provide a generic technology transfer plan.

2.2 Technology Transfer Planning Considerations

In the early planning phase, a charter (as detailed in Section 3.1.2) may not be fully developed yet. In this case, the team should document, at a minimum, the major deliverables and assumptions not expected to change. Examples include:

- High level program deliverables such as delivery of material to clinical trials or early planning (e.g., for analytical methods)
- Agency submission strategies
- Site licensure milestones
- Budget
- Mechanism for handling changes, e.g., in scope or budget

As stated earlier, technology transfer can be considered a transfer of knowledge using well founded project management principles.

This section describes considerations for a successful transfer. For information on initial risk/feasibility assessments, see Section 5.2.

2.2.1 *Developing an Early Agreement Between the Sending and Receiving Units*

An agreement (referred to as a charter in Chapter 3) is typically high level and developed with input from sending and receiving unit Subject Matter Experts (SMEs); input is rarely from the full technology transfer team. Securing an early agreement, sometimes referred to as site selection, may be necessary to release the full resources required for detailed planning and execution.

It is increasingly common that early stages with long lead times are initiated prior to formation of the entire team. It is also often necessary to make an early assessment of HSE aspects; an example is a facility that is not capable of handling particular compounds from an HSE standpoint.

By its nature, a technology transfer requires effective management of incomplete information; consideration of information and SME availability is required to determine appropriate planning timelines.

2.2.2 *Sending Unit and Receiving Unit Working Closely*

Technology transfer planning should be initiated as early as possible. Roles and responsibilities for sending and receiving units should be defined early and updated frequently in the early planning stages. Effective planning and diligent tracking of potential issues can help to expedite technology transfer projects and prevent delays.

A plan created by collaboration between sending and receiving units can help to unify the technology transfer team and to ensure that there is agreement on deliverables, success criteria, and ownership of the transfer at different stages. Project management tools such as the RACI¹ matrix can be useful to formalize roles.

The relationship within the technology transfer team should be actively maintained. This includes cultivating the skills needed to develop the team and building trust. Partnership between sending/receiving project managers and accountable functional area leads is key to actively managing the flow of known and emerging process, method, and site capability knowledge. When the sending and receiving units are within the same company, it is important not to overlook the need to have a formal plan which includes defining roles and responsibilities from individuals and departments.

It is important to understand the critical path timetable and ensure that the technology transfer planning and execution timelines are consistent with the critical path timing. Technology transfer timing should allow for the project manager to adjust the schedule, as needed, without moving major milestones: The timeline should be realistic. Communicating an unrealistic timeline to management could result in the team's acceptance of undesirable risks in order to meet their commitment. Management on both receiving and sending units should be apprised of the timeline and potential risks and their support should be obtained.

People to people interaction should be encouraged, especially between counterparts in the sending unit and receiving unit. This is especially important where different cultures exist between sending and receiving units. Implications of this may involve extra cost and therefore require management support (e.g., providing authorization for staff to be away from their normal jobs for travel).

The technology transfer plan should be reviewed and updated (as required) on an ongoing basis. Any changes that impact the budget, timeline for major milestones, or assumptions/risks should be incorporated and approved by stakeholders to ensure alignment.

¹ **Understanding the RACI acronym [17]** – for every step of a planning project, the following should be defined:

R = Responsible	The person who is ultimately responsible for delivering the project and/or task successfully.
A = Accountable	The person who has ultimate accountability and authority; they are the person to whom "R" is accountable.
C = Consulted	Someone whose input adds value and/or buy-in is essential for ultimate implementation
I = Informed	The person or groups of individuals who need to be notified of results or actions taken but do not need to be involved in the decision-making process

2.2.3 Clear Understanding of Roles and Responsibilities for Both the Sending and Receiving Units

A clear understanding of roles and responsibilities for team members, from both the sending and receiving units, serves to minimize redundancies and oversights. Knowing what is expected by other team members can increase accountability and help to minimize confusion and conflicts.

Additional recommendations include:

- Performing an assessment of the team capabilities relative to the skills required to complete tasks for which team members are accountable
- Defining decision rights (i.e., who will make the decision regarding particular aspects or differences of view)
- Defining clear communication routes both within the team and external to the team using, e.g., meetings, shared network or other project sites, meeting minutes
- Documenting roles and responsibilities with appropriate project management tools such as a RACI matrix – for additional information, refer to *ISPE Good Practice Guide: Project Management for the Pharmaceutical Industry* [17]

2.2.4 Effective Knowledge Transfer

It is very important that both sending and receiving units discuss and agree the knowledge to be transferred – scientific, regulatory, operational (including tacit knowledge), business, and cultural. Knowledge management is becoming an increasingly important topic.

Scientific aspects include, for example:

- Descriptions of the chemistry, physical chemistry, and biology involved in the design of the process
 - Understanding of process description/rationale/history, process flow diagrams, unit operations, scale, material transfers, etc. from dispensing through to packaging
 - Understanding what is important to control for both drug substance and drug product manufacture (see ICH Q8(R2) [3]) including, as appropriate, impact on packaging)
- Ensuring CQAs are understood by both sending and receiving units
- Ensuring analytical technology required to measure process performance is defined and enabled
 - For example: analytical system suitability and sample type qualification, receiving unit suitability/capability/applicability, and availability of technologies to be used for test methods transfers such as High Pressure Liquid Chromatography (HPLC) equipment, columns, etc.
- Understanding the requirements of the receiving unit, including facility fit, equipment constraints, and HSE (e.g., safe handling of the drug substance, drug product, and in-process intermediates)
- Transferring the control strategies from sending to receiving unit and operationalizing it
 - **Note:** even for legacy products, regulators are increasingly expecting a QTPP, CQAs and control strategies to be in place (e.g., FDA internal document MAPP 5016.1 [19])
- Being clear on CPPs and material attributes for each unit operation and understanding the impact of unit operations on CQAs, the expected and acceptable operating ranges and appropriate limits (including design space, if used)

- Taking into account when multivariate approaches are used (e.g., a design space is developed, a model employed, PAT tools used for feed forward or feedback, real time release testing, etc.) and/or continuous manufacturing
- Potential sources of variation

Regulatory aspects include, for example:

- Compliance by both sending and receiving units with regulatory requirements in the country they operate in and the country where the product will be supplied to
 - Individual countries may have their own variation guidelines
 - For example, some countries may have specific requirements for conducting additional bioequivalence studies
- Ensuring validation is carried out appropriately including lifecycle approach
- Ensuring adequacy of the Quality Management System (QMS)/Pharmaceutical Quality System (see ICH Q10 [1])
- Taking into account that some regulations are slightly different in different countries (e.g., acceptability of three validation batches versus justifying the number of batches)
- Within both sending and receiving units, checking that there are no regulatory changes in progress that could later impact the implementation of the transfer

Operational aspects (including tacit knowledge) include, for example:

- Understanding the facility and utility requirements, e.g., facility fit, utility capacities, particular requirements that may be needed such as for aseptic facilities (classified areas, environmental controls, etc.)
- Understanding operator training and/or qualification requirements for the technology of the process, particularly if the receiving unit is less familiar with the technology or process
- Taking into account that equipment principles may differ (e.g., mixers or dryers may use different engineering principles to deliver the required homogeneity or dryness)
 - A check should be performed to ensure that there are no regulatory implications, e.g., impact on stability
 - Where needed, provide calculations, special instructions for scale-up, equipment equivalency reports, etc. if available
- Developing new manufacturing instructions and SOPs
 - The sending unit would normally concentrate on serious inaccuracies, omissions, or strategic problems with the content in the receiving unit's batch records or SOPs (e.g., not changing the layout)
- Understanding HSE requirements, e.g., need for containment or operator protection
- Putting maintenance procedures in place
- Understanding differences in operational principles, for example:
 - Number of shifts per day (e.g., three shifts versus day shift only), number of working days per week, whether shifts can be run consecutively, etc.

- Automated versus manual operation
- Use of PAT tools
- Different scales
- Different batch sizes
- Different process flows
- Different sampling techniques
- Gravity flow versus horizontal transfers of powder
- Understanding tacit knowledge, i.e., knowledge that may not be explicit or documented but shows actual practices for doing certain tasks
 - Examples include scalability, the way a vessel is charged, or the way an analyst carries out a particular test
 - This is particularly important regarding such knowledge from the sending unit
 - It is also important that this knowledge is documented
- Assessing if long term planning is needed to obtain raw materials, e.g., due to import license restrictions
- Reviewing if operators from the sending unit can work on the receiving unit's site
 - This can be beneficial in enabling knowledge transfer and reducing errors on first batches
 - It is recommended to assess implications such as obtaining work visas, training, concerns by the receiving unit from Quality Assurance (QA), HSE, or regarding intellectual property

Business aspects include, for example:

- Importance of the product being transferred, which may differ from sending to receiving units, e.g. the profitability of one might be different to another, the transfer may be critically important to one company to release space for a more highly valued product, etc.
- Determining who pays for what (e.g., new equipment, training of personnel, etc.)
- Determining responsibility for capital; specifically, who pays for the investment itself, who owns the asset in terms of responsibility for depreciation, and for CMOs, whether that asset can be only be used by one client or is able to be used by multiple clients

Cultural aspects are an important but difficult area to assess. Gaining an understanding of a company or country's culture can significantly contribute to the success of a technology transfer. Some cultures may be procedural, some may be hierarchical, some may be unstructured, some may be relationship dependent, etc. Language can be a factor; for example, while English may be the global language of a company, the local language for SOPs and operators may be different. Some cultures (even within a company) can be very different between units; for example, quality systems may have matured differently in practice, particularly where a company has recently taken over a site. Technology transfer teams should be sensitive to and aware of potential implications where culture may be significantly different and maintain an awareness to ensure similar understanding at both units. Refer to the *ISPE Cultural Excellence Report* [13] which provides a useful background.

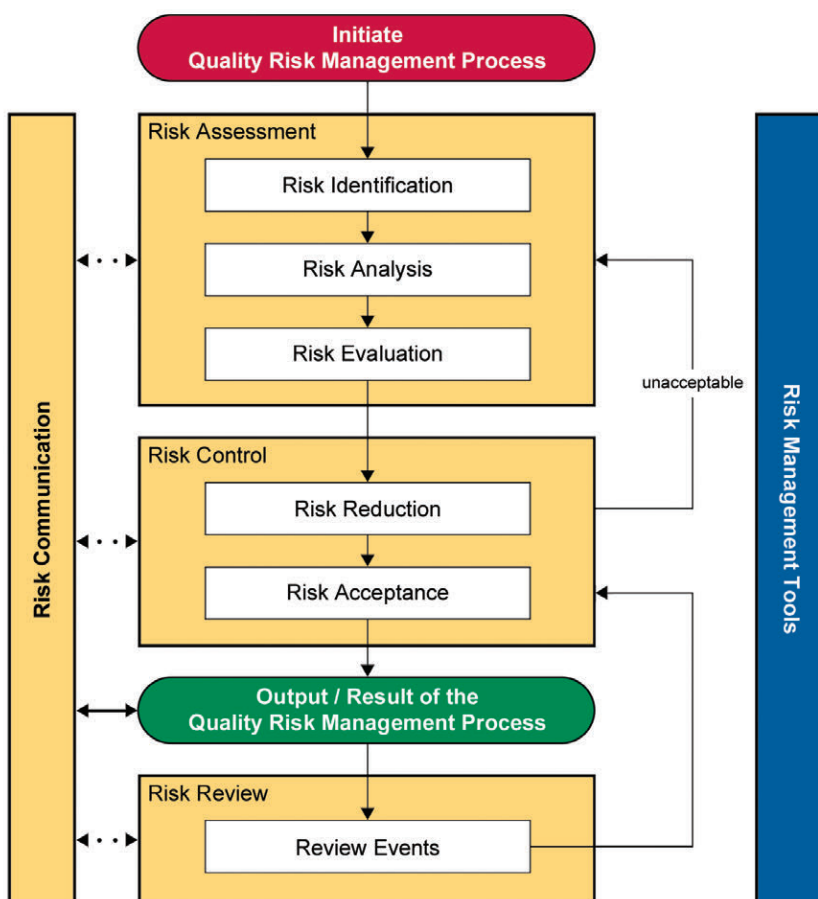
2.2.5 Information Package

A sufficiently complete technology transfer package of information should be developed to meet the requirements of the technology transfer. Refer to Chapter 3, Chapter 8 (Appendix 1), and Chapter 13 (Appendix 6) for additional information.

2.2.6 Quality Risk Management

QRM is integral to technology transfer and should follow ICH Q9 [4] principles (see Figure 2.1) or similar. It is important that teams are rigorous in their application of Q9 [4] and spend sufficient time during the initiation phase to ensure full understanding by both sending and receiving units of the purpose of the QRM exercise. Once the initiation phase is completed, a detailed risk assessment should be carried out (e.g., using tools such as cause and effect matrices, Ishikawa (fishbone) diagrams, gap analysis, and FMEA). After agreement on acceptable and unacceptable risks, then the unacceptable risks should be mitigated to an acceptable level and then controlled through a defined risk mitigation plan. This could involve experimentation and/or facility/equipment modifications and, when successfully implemented, will help to minimize risk and negative factors in the transfer process.

Figure 2.1: Flow Diagram from ICH Q9 Quality Risk Management [4]



QRM is an iterative activity. All technology transfer projects require risk assessment. Existing risk assessments may need to be adapted to acknowledge changes in risk during the technology transfer. It is helpful to have a QRM plan if there will be multiple risk assessments. Note that there can be several types of risk assessment – for the project, the process, the product, the equipment, etc. The owners and focus of the risk assessments can be different. Normally, the project manager would own the project risk assessments and the technical team would own the technical risk assessments.

2.2.7 Phases and Stage Gate Approach

The technology transfer project may be approached in phases (stages). Documentation of the project should include the important activities for each phase, e.g., reviews, deliverables, and projected timelines. Refer to Chapter 3 for the six phases of technology transfer.

Even in the early planning phase, there should be a mechanism for handling changes, e.g., in scope or budget. Throughout the project, stage gate reviews should be used to ensure that all critical items from the current project phase have been completed satisfactorily before moving on to subsequent phases of the project. This approach helps to ensure critical project items are completed on time and that later phases of technology transfer are not put at risk. Stage gate reviews should be attended by stakeholders and the technology transfer team.

For detailed information on the stage gate approach, refer to the *ISPE Good Practice Guide: Project Management for the Pharmaceutical Industry* [17].

2.3 Technology Transfer Success Criteria

Technology transfer is considered successful if the receiving unit can consistently produce material through the qualified process and demonstrate that quality attributes have been maintained through process monitoring and analysis of the material produced.

Simply stated, technology transfer can be considered successful if the receiving unit can routinely reproduce the transferred product, process, or method against a predefined set of specifications as agreed upon with the sending unit and/or development unit.

A comparability exercise may be completed as an assessment of sending versus receiving process/method performance. Interim success criteria are developed to track progress toward these goals. Success is ultimately demonstrated by regulatory agency licensure in the desired region(s). In addition, business performance parameters are established to balance risk versus cost, including resources.

Evaluation of the success of a technology transfer should be based on a pre-established set of criteria, which are evaluated as the project progresses. These criteria may be used to track progress of the transfer into subsequent phases and hence manage risk.

Industry R&D productivity, global product introductions, and increased generic competition (including biosimilars) are driving increased emphasis on establishing meaningful success criteria. These factors impart pressure by increasing the number of transfers, increasing global filing deliverable complexity, and reducing transfer duration. These pressures are driving innovation in the establishment of site criteria and measurement methods; hence, portions of the success criteria are transferred with the process or methods rather than established at the receiving unit. In addition, the need to increase the rapidity of measurements and subsequent decision cycles has created drivers for changes toward real time monitoring and on the floor measurement.

Success criteria usually take into account the business situation and product requirements, for example:

- Stage within the product lifecycle
- Availability of product and process knowledge
- Experience of the sending units and receiving units
- Number of sites involved
- Whether it is a transfer between internal sites or to an external site

From a business perspective, the success of a technology transfer is based on efficiently meeting the requirements of product quality, patient safety, and efficacy, and business requirements. Business requirements may include the following:

- Cost, including capital cost, expense and Cost of Goods Manufactured (COGM) targets
- Capacity/volume
- Equipment and facility capabilities
- Time frames
- Risk management
- Regulatory requirements or strategy, including meeting existing commitments
- Supply chain strategy

The relative importance of each of these factors should be established by the individual companies engaged in the technology transfer.

For example, when shared equipment is used in a multi-product facility, there may be additional requirements for risk assessments (e.g., cleaning validation assessments) before receiving regulatory approval for the newly transferred product to be manufactured at a receiving unit. For additional information, refer to the *ISPE Baseline® Pharmaceutical Engineering Guide, Volume 7 – Risk-Based Manufacture of Pharmaceutical Products (Second Edition)* [20].

Success criteria can take several forms and may be dependent on the technology being transferred and the phase of development in which the transfer takes place. The criteria should be measurable and achievable. Success criteria may include:

- Evaluation of the technology performance
- Adherence to the project timeline
- Adherence to the budget

Success criteria can be developed using data from the sending unit. The data could be quantitative (e.g., statistical analysis or other techniques) or non-qualitative (e.g., gel band shifts or mass spectra fingerprinting) and then transformed into quantitative values (e.g., assay endpoints). They can be based on the technology transfer team's understanding of the process, the risk identification/gap analysis and remediation, and other inputs such as regulatory and business requirements. The data set from the sending unit should be used to create a relevant set of success criteria for the receiving unit that allows the receiving unit to demonstrate a successful technology transfer. The data set to be used by the receiving unit should be identified during development of the success criteria. The data may be part or all of a package of comparability or validation analyses developed from the execution of the technology at the receiving unit as a part of development.

Specific success criteria should be documented in the technology transfer plan. Main aspects may include:

- Process performance – comparing in-process data (either traditional or PAT generated) with historical data
- Product quality that meets pre-established criteria:
 - Definition of data sets to be used for comparability analyses (e.g., earlier phase clinical data, manufacturing data from the sending unit)

- Confirmation that the control strategy is executable
 - Confirmation that the product control strategy from the sending unit has been successfully delivered by the receiving unit, including meeting requirements of product CQAs and specifications
- (**Note:** If a design space has been specified, this should be confirmed within agreed success criteria.)
- Process performance as expected based on historical data
 - For large molecule, examples include cell growth rates, titers, step yields, chromatogram profiles, and impurity clearance
 - For small molecule, examples include: impurity levels (e.g., solvents, elemental impurities), quality attributes (e.g., dissolution), material attributes (e.g., particle size distribution), process parameters (e.g., compression force settings to obtain required dissolution), process yield, and throughput (i.e., process efficiency)
 - Analytical method transfer and equivalency
 - Successful routine operation of the specified process over an agreed number of batches
 - Successful routine operation of the facility and equipment with regard to operability, labor, and utilization plant occupancy times to improve Overall Equipment Efficiency (OEE) and to maximize overall operational efficiency
 - Training of staff
 - HSE objectives achieved
 - Documentation fully and satisfactorily completed within the defined timescale
 - Regulatory inspection outcomes and reviews, where appropriate
 - Regulatory submission on time
 - Facilitation and adjustment of the scope of process validation (e.g., by expanding prior knowledge of critical parameters)
 - Improvement of process robustness and efficiency (exact 1:1 transfers are rare; there are normally opportunities for optimization which could not be realized initially at a sending unit)

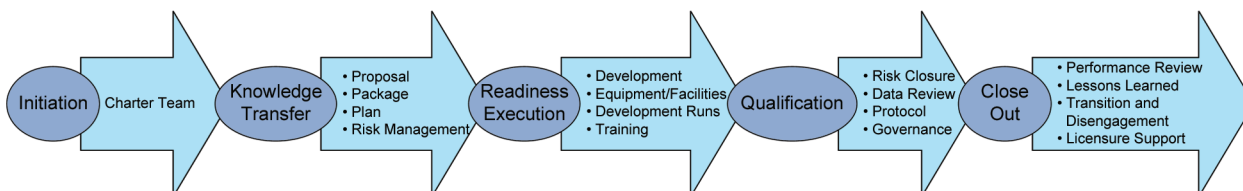
Consideration should also be made to establish longer term criteria (e.g., during process validation Stage 3 [6]) following closure of the technology transfer report. For example, technology transfer studies may fail to predict variance that is inherent in longer term evaluations of process stability. Also, there can be longer term variance from material or equipment that can be difficult to model with limited numbers of batches, even during a very robust technology transfer. Success criteria could include permitting natural material attribute variance or, if possible, intentional material attribute variance. These types of longer term criteria should be practical; consider on the one hand, historical variance if well understood by the sending unit, and on the other hand, criteria more robust than simply passing specifications. Longer term criteria should also consider unexpected excursions with scrutiny back to the closed technology transfer.

For additional information on evaluating transfer performance, see Section 5.2.5.

3 Technology Transfer Project Phases

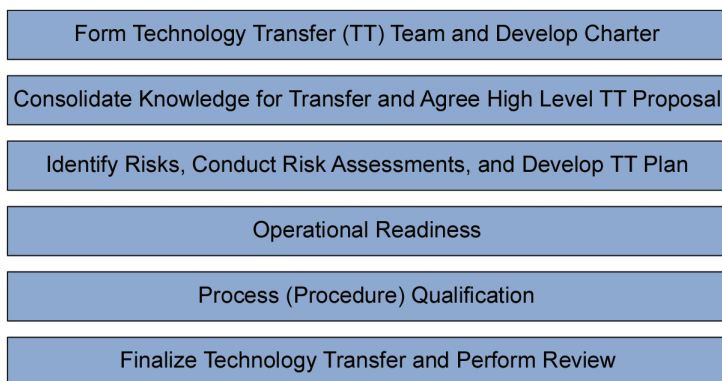
An overview of the chapter is provided in Figure 3.1.

Figure 3.1: Chapter Overview



This chapter provides a description for each of the six phases of a technology transfer. It is intended to be generic and describes general practices that apply to all transfers regardless of the technology being transferred. To note, at the time of publication, it is increasingly common for phases to overlap and/or be executed in parallel. The same principles used to manage and control a traditionally phased technology transfer can be leveraged for transfer with overlapping phases. The key principle in either case is to identify critical dependencies and control phase execution accordingly. Figure 3.2 shows the six phases of technology transfer.

Figure 3.2: Phases of Technology Transfer



3.1 Form Transfer Team and Develop Charter

The initiation phase of technology transfer should establish the team, strategy, and goals of a project. Sending and receiving units should establish an integrated team of the required SMEs from the functional areas involved in the transfer. This team should develop a technology transfer charter to capture the goals, milestones, and roles and responsibilities for the project.

3.1.1 Establishing a Team

A formal technology transfer team should be established. The team structure, roles, and responsibilities should be identified. Team structure should include leadership from both sending units and receiving units, along with SMEs from the relevant functional areas. The team structure, roles for SMEs, and priorities will vary depending on whether the team is dedicated to:

- Analytical methods
- Drug substance

- Drug product

At the start of the technology transfer program, key stakeholders, technical leads, and project managers should be identified. An overall project manager is usually responsible for delivery of the technology transfer and should coordinate activities such as finance, quality/regulatory, and materials management. Project managers may also be assigned within a functional area and will work closely with the overall project manager.

Technical leads are usually responsible for ensuring that project managers have the technical information to enable delivery of the technology transfer. These leads focus on the technical aspects of the technology transfer within their area of expertise and accountability. Depending upon the complexity of the project, a technical lead and project manager may be the same person. If the lead serves this dual role, it is important to ensure that staff who are trained in a technical discipline have the proper project management training and experience required to run the project. In addition, project management responsibilities cannot be neglected when competing priorities arise, for example, if the lead is needed for technical problem solving.

Team leads should assemble the technology transfer core team by including required SMEs. The composition of the core team is determined by the process being transferred and the required expertise to support the transfer. The core team should include representation from both the sending and receiving, as appropriate. Examples of functions represented in the core team include:

- Analytical sciences
- Analytical/Quality Control (QC)
- Engineering
- HSE and sustainability
- Late stage development
- Manufacturing operations
- Manufacturing technical
- Material management
- Planning
- Process development
- Project management
- QA
- R&D
- Regulatory affairs
- Supply chain

Project stakeholders, such as senior management or budget managers, can provide oversight and guidance to the core team. Examples of functions represented by project stakeholders include:

- Finance

- Manufacturing
- Process development
- Program management (commercial)
- Quality
- R&D
- Regulatory affairs
- Technical services

Technology transfer team leads and project stakeholders, across both sending and receiving units, should define the appropriate governance and controls for a project. Generally, this would cover the following:

- Scope of the project
- Timelines and key milestones
- Resources and budget
- Success criteria
- Reporting and escalation structure
- Key decision gates/approval process
- Change and risk management processes
- Quality management

Communication between the members of the team can be more effective when team members:

- From both units have a similar level of knowledge and experience of the techniques involved
- Have good team working skills
- Have the time to ensure that actions identified in the risk/gap assessment process are progressed
- Are familiar with the tools and techniques that support an effective knowledge transfer
- Define mutually accepted means of communication and collaboration – for example, geographically diverse teams may want to schedule face-to-face meetings for kickoffs and major milestone reviews, interspersed with regular web enabled teleconferences
- Acknowledge and manage cultural differences so as not to disrupt communications – team leads in international transfers will have an additional role of monitoring the effectiveness of team members at all levels and resolving communication impediments resulting from cultural differences

A leader who can promote an integrated team with the members from both the sending unit and the receiving unit can also help facilitate the process.

3.1.2 *Developing a Charter*

The technology transfer team may develop a technology transfer charter. The charter can include:

- Assumptions and constraints
- Sites impacted (sending and receiving)
- Scope
 - Includes overview of the project and business drivers
 - Items that are out of scope are equally important to document in the charter
- Objectives and technical success criteria (see Chapter 2)
 - Examples include number of batches required, anticipated yield, successful registration and launch, etc.
- Roles and responsibilities
 - Clear understanding of expectations for each leadership role on the team and the deliverables for the respective functional area, including documentation, testing, disposition, and stability requirements
- Technology transfer team
 - Define who is within the team from each of the units, potential sub-team requirements, and understanding of key stakeholders
 - Should also include details of meeting frequency
- Governance – definition of decision rights and escalation path
- High level technology transfer plan²
 - Timescales of activities and resource requirements from each of the functional groups in across the sending unit and receiving unit
 - Communication strategy
 - Risk assessment review (including HSE)
 - Technology transfer documentation expectations aligned with individual responsibilities
 - Analytical transfer process and timelines
 - Commissioning and validation of any additional technology or infrastructure that is required
 - Manufacturing plan and sampling requirements
 - Data review plan, including deviation (non-conformance) reporting obligations between sending and receiving units

² Development of a detailed execution plan is covered in Section 3.3.3; some elements of the plan may be noted as To Be Determined (TBD) during charter development and flagged for completion in the develop technology transfer plan phase.

Note: Typically, deviations are reported back to the sending unit to facilitate support in review and for applicable development of corrective actions. However, if the sending unit is, for example, in production, utilizing methods transferred, under regulatory agency review, etc., then sending to receiving reporting will be equally important.

- Regulatory strategy
- Change control procedure
- Technology transfer completions of and formal transfer to clinical and/or commercial operations (release of sending technology transfer team members)

The technology transfer charter should be reviewed and approved by the appropriate stakeholders, executive sponsors, and senior management from both the sending and receiving units.

Note: The technology transfer charter and proposal may be either the same document or the charter may be versioned, depending on the complexity of the technology transfer project.

3.2 Consolidate Knowledge for Transfer and Develop Technology Transfer Proposal

3.2.1 Technology Transfer Proposal

A technology transfer proposal may be useful to define, facilitate review, and garner agreement of incomplete elements of the charter. In addition, prior to developing a detailed execution plan, a proposal can be used to develop detailed requirements and acceptance criteria for either key, or yet undefined, aspects of the plan.

The items listed below are recommended for inclusion in the technology transfer proposal; each team and project will likely need additional information specific to that project.

- HSE required assessments and known impacts
- Overview of project and business drivers
- List of team members and management/budget approvers (stakeholders)
- Broad objectives and deliverables
 - These may include projected clinical manufacture (successful number of runs), other GMP batches, any agreed upon process upgrades or improvements in yield, and successful registration and licensure
- High level timeline and resources needed
 - The project should be divided into phases, with a review and “approval to proceed” at the end of each phase (e.g., completion of technology transfer proposal, completion of engineering runs)
 - The timeline should be realistic, and not assume 100% success
 - Identify significant capital requirements and estimated Full Time Equivalent (FTE)
 - Identify which unit is responsible for funding elements of the project
- Issue resolution pathways and governance, including escalation

- Validation strategy
- Regulatory strategy
 - Plans for product/process comparability, stability, and process validation
 - Meetings with regulatory agencies, filing dates, etc.
- Assumptions
 - List assumptions that are included in the proposed timeline
 - For example, availability of raw materials or process intermediates, successful transfer of analytics, the degree to which process changes will be acceptable, compatibility of data systems, process fit with minimal facility modifications, sufficient site utilities, no significant impact on site layout (e.g., material handling, personnel routes, safety)
- Potential risks to the project – high level risk assessment
 - For example, competition for FTE and resources from other programs, unfavorable clinical or regulatory outcomes, gaps in process understanding when changes and scale are within the in scope of a technology transfer, inability to mitigate significant gaps, inability to mitigate facility fit, limitations to available analytical support, product comparability issues
- Identification of information that is needed for the technology transfer package
- Identification of opportunities for members of the technology transfer team (e.g., receiving unit personnel) to observe the process at the sending unit to pick up any tacit knowledge (nuances or hands-on information which are not detailed in manufacturing instructions) and visual documentation (e.g., wet massing consistency, solution clarity)
- Requirements for disposition, storage, shipping, and forward processing, such as drug substance to drug product

Note: The technology transfer charter and proposal may be the same document, depending on the complexity of the technology transfer project. Where a drug substance or drug product has received a marketing authorization, the regulatory strategy may be a key contributory factor in the strategic intent of the project.

Both the sending unit and the receiving unit should review and agree on the technology transfer proposal. A summary of the success criteria, as described in Chapter 2, is useful to ensure alignment across organizations and at different levels of management.

3.2.2 Technology Transfer Package

The technology transfer package should be organized efficiently to provide easy access to necessary information. It should also be comprehensive, so that a receiving unit can become self-sufficient in running a process or analytical procedure.

Basic requirements for the technology transfer package include, e.g.:

- HSE related requirements
 - It is prudent to prioritize HSE impact assessments early in the transfer as these impacts may require long lead activities such as facility modification, regional licenses, and new training and monitoring programs

- Business requirements
- Product specific requirements, particularly CQAs and control strategy and how these will be delivered for both drug product and drug substance at the receiving unit

Note: It is not the role of technology transfer to identify quality attributes and process parameters and their relationships; this is the basis of the control strategy which is typically defined during process development. The control strategy is required to be available to the receiving unit to provide the scientific rationale which supports the manufacturing process and supporting analytical methods.

- Process flow diagrams, unit operations, parameters and material attributes, design space (where used), process trends, and detailed historical data (including the sequence and justification of any process changes), and risk assessments and identified CPPs (e.g., set points and ranges) and CQAs to ensure the control strategy is executable
- Facilities capabilities assessment relative to the ability to implement and consistently execute requirements of the control strategy

In addition to the basic requirements described above for the technology transfer package, additional items should be incorporated as the technology transfer progresses.

The technology transfer team should review the completed technology transfer package and request SME input, as appropriate, to ensure that all relevant knowledge is captured. The team should also summarize the available knowledge and conduct a high level technical risk assessment.

The technology transfer team should ensure that the receiving unit understands the information that they have available and can obtain clarifications as necessary. The knowledge transfer should take into account the level of expertise at both the sending unit and the receiving unit.

For transfers to an external partner or CMO, the transferring organization should determine what kinds of intellectual property it would consider to be confidential and determine how to redact documents appropriately or extract the key information needed by the receiving unit for transfer. See also Section 1.2.3.

The technology transfer package information will be used by the team members to work on a detailed process description and list of requirements for the receiving unit to execute the process. For example, the receiving unit process description may include scale-up information not provided by the sending unit. The team should then work through this list as part of a gap analysis, to identify, assign scores (if needed), and propose mitigation activities for gaps. The information gathered from the process description and gap analysis should be incorporated into a detailed technology transfer plan.

3.3 Identify Risks, Conduct Risk Assessments, and Develop Technology Transfer Plan

Following approval of a proposal for the technology transfer and exchange of the technology transfer package, the transfer team should perform risk assessments on identified gaps between the process or procedure requirements and the receiving unit capabilities and practices.

The technology transfer package can be used by both units to initiate risk assessments and begin developing the technology transfer plan for process or method implementation, along with the information, data, or work that will be required to ensure the technology can be successfully executed at the receiving unit. These assessments should compare the process or procedure history with the receiving unit capabilities and operations to identify gaps or misalignments that will require modifications.

In addition, the receiving unit should perform assessments of the following:

- Process/method performance and validation packages
- Raw materials/reagents for supply risk
- Impact of incoming technology
- Impact of changes needed as part of the implementation

This planning phase concludes once the sending and receiving units have completed the required assessments and have initiated plans to either remediate identified risks or receive risk acceptance from an appropriate governance.

Planning and execution of a technology transfer should include a comprehensive risk assessment process (i.e., risk identification, risk analysis, and risk evaluation as per ICH Q9 [4] or similar), followed by risk control (i.e., risk reduction and risk acceptance) and development of a detailed action plan to mitigate risks.

As part of a technology transfer, QRM is the documented procedure by which differences between sending unit and receiving unit can be identified and managed. Risk assessment is the process by which the criticalities of these differences are qualitatively or quantitatively estimated and prioritized. Once key gaps that require mitigation of risk are determined, a specific action plan for each gap should be defined and performed as part of the technology transfer execution.³

The aim of QRM is to lower risks to acceptable levels. Where this is not possible or readily achievable, the risks are presented to the stakeholders for their approval to proceed “at risk” to the process qualification stage. Any differences between the sending unit and the receiving unit have the potential to increase risk to the receiving unit’s ability to demonstrate product realization, cause delays, increase technology transfer costs, and have negative business impacts. Sufficient time should be provided before technology transfer execution to identify and address differences. The sending unit and the receiving unit should perform these activities to help to improve knowledge transfer. These activities can promote teambuilding and improve future communication during later stages of a technology transfer.

It is usually preferable to address issues prior to the process qualification exercise, as opposed to during. For instance, if a process change is required due to conditions/constraints at the receiving unit, risk could be better defined and potentially mitigated by conducting studies in the small scale process model to examine the effects of the change.

It is advised that risk identification, risk analysis, and mitigation be conducted as early as possible since some risk mitigation activities may have long lead times and thus could significantly delay technology transfer. Although site selection is not discussed in this Guide, facility fit and site expertise are important factors to consider as they can have significant impact on the timeline and costs.

This risk assessment should be used to define the overall transfer approach.

3.3.1 Identifying Risks

As noted in Section 1.2, effective knowledge management (including tacit knowledge) is critical for effective risk management. Teams are advised to critically review information and knowledge utilized in risk identification, e.g., gaps in development reports.

Identification of risks is typically performed by appropriate SMEs and ad hoc members from the sending unit and the receiving unit (i.e., process/technical experts, manufacturing, quality, facility and process engineers, automation, materials/procurement, HSE, analytical, Chemistry, Manufacturing, and Controls (CMC) regulatory, etc.). This

³ In the case of site to site transfers, an assessment and mitigation of differences in the QMS between sending unit and receiving unit should be performed. Typically, this is done as part of the quality audit. Details of these activities are outside the scope of this document.

is usually achieved through a series of joint and breakout meetings with the goal of capturing all differences or similarities between the sending unit and the receiving unit and may include a trained facilitator. Where available, data sources and level of uncertainties should be captured.

Effective risk identification/gap analysis requires availability or completion of the following:

- A sufficiently complete technology transfer package reviewed prior to meetings
- Dedicated input from team SMEs, e.g., for execution of risk assessment practices
- Detailed simulated runs of the process covering topics such as those listed below. Gaps noted during the simulated run exercise should be captured and further evaluated through the risk management program. It is recommended that the team work step-by-step through actual batch records or other descriptive documents such as those for:
 - HSE standards and regional requirements
 - Equipment, utilities, and facility detailed descriptions and drawings
 - Instrumentation, control, and automation
 - Operating procedures (sample handling, timing of key process actions)
 - > For example, how long it takes to collect a bioreactor sample and take a measurement, the instrumentation used for off-line tasks, avoiding product shear through high speed stirring/vortexing
 - Resources projections and availability (people/FTE)
 - Materials and consumables, including review of suppliers and ability to supply (quality and quantity), extractables, and leachables
 - Analytical support requirements
 - Cleaning requirements for equipment (including ancillary processing equipment) and facility
 - Process modeling to help identify facility engineering modifications
 - Documented control strategy, including understanding of product CQAs, the unit operations, their CPPs and material attributes, and (if used) the design space to confirm the control strategy is executable
 - Opportunities for continual improvements
- Process and method reviews or walkthroughs by sending units and receiving units to jointly identify all differences or gaps that should be assessed
 - This exercise can also be beneficial to knowledge transfer and provides opportunities for the sending unit to observe and ask questions regarding critical manufacturing operations
 - The walk throughs can utilize current documentation, such as batch records, and systems, such as automation sequences, to guide the team stepwise through the process or method
- Assessment of the capability and expertise of the receiving unit (in addition to resource gaps)
 - Appropriate training programs should be developed to address potential technical or operational gaps

The level of risk should be reviewed and endorsed by the respective risk owners on the technology transfer team. Residual risk (i.e., risk remaining after remediation) should be proactively communicated to leadership. The role of leadership is to either accept the residual risk or require migration actions prior to proceeding to subsequent phases of the transfer.

The risk identification/gap analysis is a living document which should be updated on an ongoing basis, as further information becomes available.

3.3.2 Risk Analysis and Evaluation

Risk analysis and evaluation is a process by which the criticalities of identified risk are qualitatively or quantitatively estimated and prioritized (see ICH Q9 [4] and the *ISPE Guide Series: Product Quality Lifecycle Implementation (PQLI®) from Concept to Continual Improvement* [11]). Risk analysis and evaluation should be applied to identified risks that potentially have a direct or indirect impact on HSE, CQAs, CPPs, and process performance. Where there is insufficient knowledge or data to judge comparability of the potential risk between the sending unit and receiving unit, a systematic, proactive method for evaluating how that risk could impact the process (e.g., FMEA) should be used to assess the risk and whether mitigation is needed.

Steps to assess risks typically involve identifying potential failures, likelihood and severity of each potential failure, ability to detect failure, followed by determining the overall risk using some form of qualitative (as exemplified in Figure 3.2) or quantitative estimation methodology. The rationale for ratings assigned for likelihood, severity, and detection should be documented. Once the overall risk level is estimated for each gap, the team should determine the need for risk mitigation based on acceptability of risk and then prioritize activities.

Based on the example risk estimation matrix provided in Figure 3.3:

- An overall risk level is **low** could translate to an acceptable risk in which case mitigation is not required; however, the technology transfer team may propose mitigation to further reduce the risk.
- At risk level **medium**, the risk may be acceptable and either justification is documented, or mitigation is required.
- If the risk level is **high**, risk is not acceptable, and mitigation is required to reduce risk to an acceptable level. The team should determine appropriate actions, e.g., facility/equipment modification or acquisition, laboratory studies, or gathering of additional information.

Figure 3.3: Risk Estimation Matrix

		Severity		
		Minor	Moderate	Critical
Likelihood of Occurrence	Certain	Medium	High	High
	Average	Low	Medium	High
	Remote	Low	Low	Medium

Identified risk mitigation activities should be captured in the technology transfer plan with specific deliverables (what, by whom, and when). Risk should be reassessed after mitigation actions are established; risk that remains after mitigation is the residual risk. Residual risk should be captured in the technology transfer plan and communicated to management.

The results of the completed residual risk assessment should be documented in the technology transfer package.

Based on the assessment of risk, the required actions may vary widely, for example:

- Simple transfer of the written procedure with no formal qualification required
- Exercise that involves confirming the system suitability criteria are achieved in the receiving unit
- Detailed analysis of the difference in ways of working between the units (operational risk assessment) and formal qualification that the method is delivering fit for purpose data in the receiving unit

For drug product and drug substance, the goals of the risk assessment/risk identification would normally include:

- Confirming that the technology transfer risk assessments considers how quality attributes, process parameters, and material attributes will be achieved for both drug substance and drug product and that any implications on the control strategy are assessed
- Ensuring the link between the drug product CQAs and the drug substance material attributes and process parameters are understood to ensure the technology transfer will be appropriately achieved, and then identifying gaps and the potential impact
- Identifying and prioritizing the technology transfer strategy and required resources

Examples of quality attributes and process parameters to considering during the risk assessment are shown in Tables 3.1 and 3.2, respectively. Table 3.3 provides examples of HSE variables to review.

Table 3.1: Examples of Quality Attributes to Consider During the Risk Assessment

Drug Substance	Biologics Drug Substance	Solid Oral	Parenteral
• Assay • Bulk density • Color • Impurities • Limits of Detection (LOD) • Particle morphology • Particle size • Residual solvent • Solution clarity	• Protein content • Aggregates • Host cell protein • Biopotency • Endotoxins • Sterility • Peptide map • Residual DNA • Acidic species	• Blend potency • Blend uniformity • Bulk density • Content uniformity • Disintegration • Dissolution • Final potency • Flowability • Foreign matter • Particle size	• Appearance • Assay • Endotoxins • Identity • Impurity • O₂ in headspace • Particulate matter • pH • Sterility • Volume

Table 3.2: Examples of Process Parameters to Consider During the Risk Assessment

Drug Substance	Biologics Drug Substance	Solid Oral	Parenteral
- Agitation speed - Distillation time - Drying time - Equipment configuration - Order of addition - Pressure - Reaction temperature - Reaction time - Regulatory starting material flowability - Stoichiometry	- Air sparging rate - Culture transfer rate - Dissolved oxygen - Gas humidity - Hold time - Incubator temperature - Nutrient feed rate - pH - Seeding density - Temperature	- Agitation speed - Airflow - Ejection force - Holding time - Impeller speed - Lubricant particle size distribution - Mill speed - Mixing time - Sieve size - Specific volume	- Airflow - Drying time - Filtration time - Gas humidity - Holding time - Mixing speed - N₂ flow rate - Order of addition - Shelf temperature - Sterilization temperature

Table 3.3: Examples of HSE Variables to Review

Category	Example	Notes to Consider
Environmental	Waste water permitting	Often a long lead time item
	Waste stream management	Local interim storage
Operator exposure	Personal protective equipment requirements	Requires training and inventory management
	HSE driven material flows and isolation requirements	Co-storage of new materials required for transfer
Safety	Inerting chemical plants	Required for volatile solvent handling
	Hazard analysis of new non-routine operations	Building this into every phase of the transfer

There are various methods and approaches to capture the risk identification/gap analysis output. Examples are provided in the appendices:

- FMEA – refer to Chapter 12 (Appendix 5)
- Fishbone diagram (Ishikawa) – refer to Chapter 13 (Appendix 6)
- Mind mapping diagram

On completion of the risk assessments and management plans, a review of the overall technology transfer plan should be performed to ensure that all required mitigation plans are included. Specifically, evidence of adequate risk reduction should be included in the plan.

3.3.3 Technology Transfer Plan

During development of the technology transfer plan, additional team members may be added; their roles and responsibilities should be clarified.

The items listed below are recommended for inclusion in the technology transfer plan; each team and project will likely need additional information specific to that project:

- Scope and objectives
 - Define the point where technology transfer ends (e.g., successful operation of a given number of clinical production runs, completion of process validation)
 - Define any necessary modifications to the process
- Resources and budget
 - FTEs aligned to required SMEs and competencies, e.g. project management (see Section 3.1), materials, capital
- Timeline and milestone dates
 - Sequence of activities, stage gates or review points, other key milestones
- Roles and responsibilities
 - Clarify/update as needed
 - Identify additional FTE resources needed from both sending unit and receiving unit (e.g., supply management, technical services, SMEs)
 - Sending team on-site support at the receiving unit
- Deliverables and acceptance criteria
- Documentation requirements, such as protocols and reports
- Assumptions, constraints, risks
 - Elaborate on what was presented in the technology transfer charter/proposal
 - Include information gathered during the risk identification/gap analysis
- Detailed risk mitigation plan to address items identified in the gap analysis
- Work plan and goals for the technology transfer process
 - For example, facility modification if needed, equipment installation and testing, buffer/materials preparation, shakedown and engineering runs
- Work plan and goals for development studies to be implemented at either the receiving unit or sending unit, for example:
 - Small scale and/or pilot scale demonstration runs to gain experience with the process
 - Development/characterization of process changes that will be implemented at the receiving unit
 - Studies to model acceptable equipment performance (mixing, temperature set point differences)

- Satellite studies to be conducted in parallel with the initial full scale batches
- Equipment details, e.g., need for ancillary equipment, critical parts or supplies, any demonstration studies required
- Supply chain and cold chain logistics – lead times, shipment, and licenses in preparation for process qualification
- Training requirements
- Updated governance structure and reporting obligations

The technology transfer plan should be updated to accommodate new information or significant changes to the timeline or resources. Any new risks encountered should be assessed and mitigated.

3.4 Operational Readiness

The goal of the operational readiness phase is to achieve a state of readiness required to move into the qualification phase, as described in Section 3.5. Both the process and methods are required to be in a state of control prior to entering qualification phase. A critical review of the operational readiness should be performed and formally documented.

Analytical methods are required to be qualified prior to full scale process qualification in order to be able to measure process performance. In some cases, method qualification may be concurrent with process qualification; in this case, the risk to the overall qualification risk must be documented and accepted by management.

Closure of actions defined by gap analysis and corresponding risk assessments drive the requirements to complete this phase.

Operational readiness activities required may include:

- Additional process or method development
- Equipment installation, modification, or re-validation
- General commissioning, qualification and validations as needed (refer to *ISPE Baseline® Guide: Commissioning and Qualification* [21])
- Engineering runs
- Procurement
- Training runs or training of staff

Having identified gaps and risks, then subsequently prioritizing activities, technology transfer operational readiness may include the following:

- Facility modifications identified in risk identification/gap analysis, including appropriate equipment validations
- Testing of full scale manufacturing equipment to ensure proper function, e.g., mixing studies, buffer or water runs, cleaning studies, etc.