Guidance for Technology Transfer

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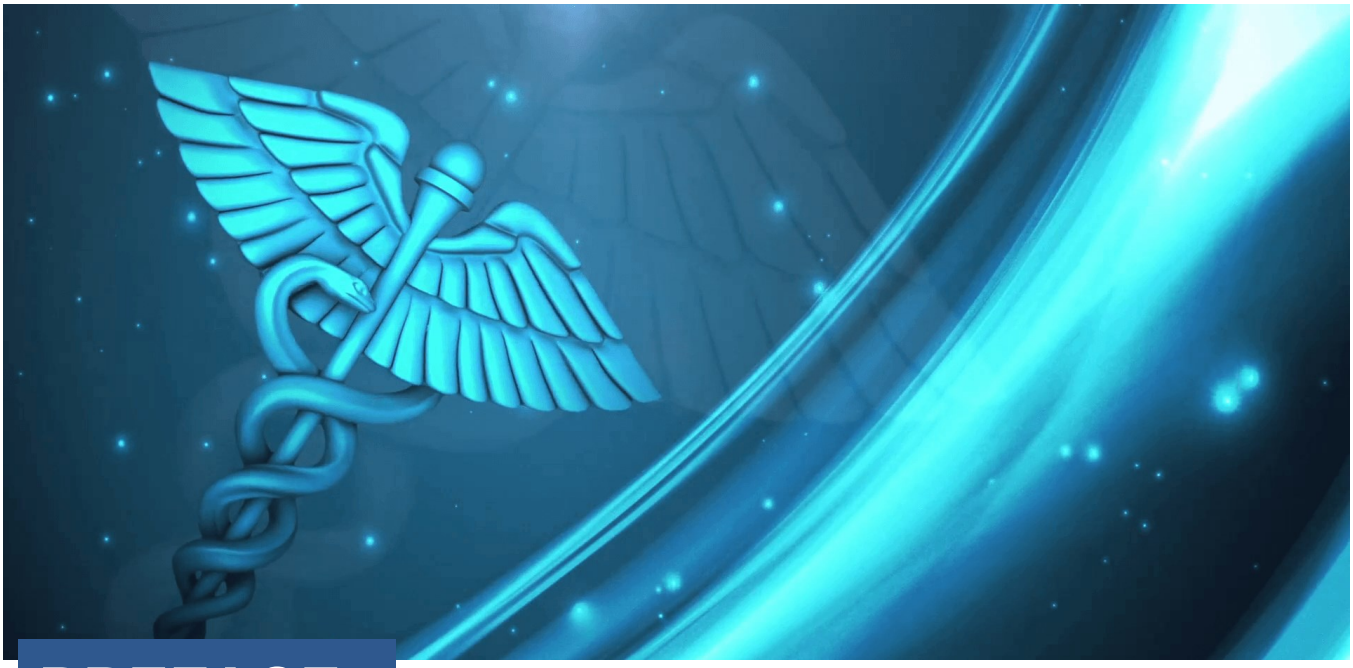


PREFACE

In April 2015, The IPA launched its Quality Forum (QF) to help Indian pharmaceutical manufacturers to achieve parity with global benchmarks in quality. The QF made a commitment to a multi-year journey to address key issues facing the industry and develop best practices.

The QF focused on several priority areas in the last four years, namely, Data Reliability, Best Practices & Metrics, Culture & Capability, Investigations, etc. It took upon itself the challenge of developing a comprehensive set of Best Practices Documents for several of these topics. In this document, we focus on best practices for Technology Transfer – Dosage Forms. We had released a comprehensive set of Data Reliability Guideline in February 2017, Process Validation Guideline and Good Documentation Practice Guideline in February 2018, Investigation of non-conformities in February 2019 and Handling Market Complaints Best Practices in February 2020.

The six participating companies in the QF nominated senior managers to study the best practices and frame the guidelines. They are: Sandeep Sharma (Cipla); Niranjan Kottala (Dr Reddy's); Arvind Raikwar (Lupin); Ashish Parekh (Sun); Uday Kumar Pandit (Sun); Rakesh Sheth (Torrent); S V Gopalakrishnan (Zydus Lifesciences) and Avinash Joshi (Zydus Lifesciences). The IPA wishes to acknowledge their concerted effort over the last 12 months. They shared current practices, benchmarked these with the existing regulatory guidance from the USFDA and other regulatory bodies such as UKMHRA, WHO, etc., developed a robust draft document and got it vetted by a leading subject matter expert and regulatory agencies. The IPA acknowledges their hard work and commitment to quality.

The IPA also wishes to acknowledge the CEOs of six member-companies who have committed their personal time, human resources and provided funding for this initiative.

This document, to be released at the IPA's Advanced GMP Workshop 2022, will be hosted on the IPA website www.ipa-india.org to make it accessible to all manufacturers in India and abroad.

Foreword

- This report outlines the approach proposed by IPA considering the ISPE and WHO guidance related to product technology transfer of dosage forms. 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.

- This guideline covers – Technology transfer from R & D to manufacturing plant (exhibit batches), Technology transfer post submission (exhibit batches to process validation) and Technology transfer from one manufacturing site to another which covers all internal manufacturing sites as well as external contract manufacturing sites.
- It is critical to the manufacture of a pharmaceutical product that those involved in that manufacture have access to the most relevant and up-to-date information. Technology transfer is the process for ensuring that this information is available when and where required.

- Technology transfer is the process of sharing of skills, knowledge, technologies, methods of manufacturing, analytical method transfer and facilities among organizations.

- Technology transfer is transferring of details of concerning formulation and analytical strategies from one area to another area that's from R&D to Production department and succeeding drug product from the laboratory scale to the production scale. In Pharmaceutical Industry, "Technology Transfer" refers to a method of victorious steps forward from drug discovery to product development, clinical trials and at last to full-scale commercialization.

- It's an organized procedure that's followed to pass the documented information and know-how knowledge gained throughout development. According to WHO outlined as a logical procedure that controls the transfer of any method alongside its documentation and professional expertise between development and manufacture or between manufacturer site. It is useful to build up dosage form in various ways because it provides efficiency in development, maintains quality of product, helps to realize a standardized process that facilitates price-effective production.

- Technology transfer is very important and critical for every stage as it helps to manufacture products consistently and improves product robustness. We suggest to review and use QbD data generated at development stage of formulation, analytical and process for technology transfer process. This will help to eliminate batch failure, minimise deviations, ensure better design of product with minimum problems and increase manufacturing efficiency and reduce waste.

1 Introduction and Background

- These guiding principles on transfer of technology are intended to serve as a framework which can be applied in a flexible manner rather than as strict rigid guidance.

- Transfer of processes to an alternative site occurs at some stage in the life-cycle of most products, from development, scale-up, manufacturing, production and launch, to the post-approval phase.

- Transfer of technology is defined as “a logical procedure that controls the transfer of any process together with its documentation and professional expertise between development and manufacture or between manufacture sites”.

- As per ICH Q10, “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.”

- It is a systematic procedure that is followed in order to pass the documented knowledge and experience gained during development and or commercialization to an appropriate, responsible and authorized party.

- Technology transfer embodies both the transfer of documentation and the demonstrated ability of the receiving unit (RU) to effectively perform the critical elements of the transferred technology, to the satisfaction of all parties and any applicable regulatory bodies.

- The ever-changing business strategies of pharmaceutical companies increasingly involve intra- and intercompany transfers of technology for reasons such as the need for additional capacity, relocation of operations, de-risk of compliance issue of 1 plant or consolidations and mergers.

- Transfer of technology requires a documented, planned approach using trained and knowledgeable personnel working within a quality system, with documentation of data covering all aspects of development, production and quality control. Usually there is a sending unit (SU) and receiving unit (RU).

- For the transfer to be successful, the following general principles and requirements should be met:
    - The project plan should encompass the quality aspects of the project and be based upon the principles of quality risk management; the capabilities of the SU and at the RU should be similar, but not necessarily identical, and facilities and equipment should operate according to similar operating principles;
    - The comprehensive technical gap analysis between the SU and RU including technical risk assessment and potential regulatory gaps, should be performed as needed;
    - Adequately trained staff should be available or should be trained at the RU:
        - Regulatory requirements in the countries of the SU and the RU, and in any countries where the product is intended to be supplied, should be taken into account and interpreted consistently throughout any transfer programme project; and
        - There should be effective process and product knowledge transfer.
- Some of the responsibilities outlined in this document for the SU may also be considered to be part of the management unit responsibilities.

2 Scope

- This guidance is applicable for all technology transfer from R & D to manufacturing plant, from exhibit scale to Validation batches or one manufacturing site to other own sites or contract manufacturing site (Site Transfer Products).

- This Guidance is also applicable for all manufacturing processes and Analytical Methods transferred from a Sending unit (SU) to a receiving Unit (RS).

Transfer Type	Sending Unit (SU)	Receiving Unit (RU)
For Registration purpose	Development Lab	Manufacturing Unit of- -Own site -CMO Site
For Higher Efficiency **(Within Manufacturing Unit)**	Manufacturing Unit of- -Own site (Small scale) -CMO Site (Small scale)	Manufacturing Unit of- -Own site (Large Scale) -CMO Site (Large Scale)
For Site transfer activity	Own site-1/ CMO Site-1	Own Site-2 -CMO Site-2

3 Purpose

- This purpose of this Guidance is to define the procedure for effective technology transfer from R & D to manufacturing site and also among the different manufacturing sites either it is own site or CMO site.

- This document gives guidance in general recommendations on the activities necessary to conduct a successful intra or inter site transfer of technology.

- The intention is to address the basic considerations needed for a successful transfer in order to satisfy the regulatory authority defined for the transfer process.

- The guidelines will be applied to manufacturing active pharmaceutical ingredients (APIs), manufacturing and packaging of bulk materials, manufacturing and packaging of finished pharmaceutical products (FPPs) and/or performing analytical testing.

- The guidelines address the following areas at the Sending Unit and the Receiving Unit:

    - Transfer of development and production (processing, packaging and cleaning);

    - Transfer of analytical methods for quality assurance and quality control;

    - Skills assessment and training;

    - Organization and management of the transfer;

    - Assessment of premises and equipment/instruments;

    - Documentation; and

    - Qualification and validation.

- Any lack of transparency may lead to ineffective transfer of technology.

4 Definitions

Acceptance criteria	Measurable terms under which a test result will be considered acceptable
Active pharmaceutical ingredient (API)	Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.
Bracketing	An experimental design to test only the extremes of, for example, dosage Strength. The design assumes that the extremes will be representative of all the samples between the extremes.
Change control	A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated status. The intent is to determine the need for action that would ensure that the system is maintained in a validated state.
Commissioning	The setting up, adjustment and testing of equipment or a system to ensure that it meets all the requirements, as specified in the user requirement specification, and capacities as specified by the designer or developer. Commissioning is carried out before qualification and validation.
Control strategy	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 materials and components related to drug substances 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.
Concurrent validation	Concurrent validation is used to establish documented evidence that a facility and process will perform as they are intended, based on information generated during actual use of the process. Based on limited number of batches for potent /slow moving molecules.

Corrective action	Any action to be taken when the results of monitoring at a critical control point indicate a loss of control.
Critical	Having the potential to impact on product quality or performance in a significant way.
Critical control point (CCP)	A step at which control can be applied and is essential to prevent or eliminate a pharmaceutical quality hazard or to reduce it to an acceptable level.
Design qualification (DQ)	Documented evidence that the premises, supporting systems, utilities, equipment and processes have been designed in accordance with the requirements of good manufacturing practices (GMP).
Design of Experiment (DoE)	Design of experiments (DOE) is a systematic, efficient method that enables to study the relationship between multiple input variables and key output variables. It is a structured approach for collecting data and making discoveries.
Design space	The multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality
Drug master file (DMF)	Detailed information concerning a specific facility, process or product submitted to the medicine's regulatory authority, intended for incorporation into the application for marketing authorization
Finished pharmaceutical product (FPP)	A product that has undergone all stages of production, including packaging in its final container and labelling. An FPP may contain one or more APIs
Gap analysis	Identification of critical elements of a process which are available at the SU but are missing from the RU.
Good manufacturing practices (GMP)	That part of quality assurance which ensures that pharmaceutical products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization
In-process control (IPC)	Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control

Installation qualification (IQ)	The performance of tests to ensure that the installations (such as machines, measuring devices, utilities and manufacturing areas) used in a manufacturing process are appropriately selected and correctly installed and operate in accordance with established specifications
Intercompany transfer	A transfer of technology between sites of different companies.
Intracompany transfer	A transfer of technology between sites of the same group of companies.
Method operable design region (MODR)	Method operable design region (MODR) is used for establishment of a multidimensional space based on method factors and settings; MODR can provide suitable method performance. It is also used to establish meaningful method controls such as system suitability, RRT, and RRF.
Operational qualification (OQ)	Documented verification that the system or subsystem performs as intended over all anticipated operating ranges.
Performance qualification (PQ)	Documented verification that the equipment or system operates consistently and gives reproducibility within defined specifications and parameters for Prolonged periods. (In the context of systems, the term “process validation” may also be used.)
Process validation	Documented evidence which provides a high degree of assurance that a specific process will consistently result in a product that meets its predetermined specifications and quality characteristics.
Prospective Validation	Prospective validation is establishing documented evidence, prior to process implementation/new product, that a system performs as is intended, based on pre-planned protocols.
QTPP	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
Qualification	Action of proving and documenting that any premises, systems and equipment are properly installed, and/or work correctly and lead to the expected results. Qualification is often a part (the initial stage) of validation, but the individual qualification steps alone do not constitute process validation.

Qualification batches	Those batches produced by the RU to demonstrate its ability to reproduce the product
Quality assurance (QA)	Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the objective of ensuring that pharmaceutical products are of the quality required for their intended use.
Quality control (QC)	Quality control covers all measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that starting materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other characteristics.
Quality planning	Part of quality management focused on setting quality objectives and specifying necessary operational processes and related resources to fulfil the quality objectives
Quality policy	Overall intentions and direction of an organization related to quality as formally expressed by senior management
Quality risk management (QRM)	Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the pharmaceutical product throughout the product life-cycle
Receiving unit (RU)	The involved disciplines at an organization where a designated product, process or method is expected to be transferred
Sending unit (SU)	The involved disciplines at an organization from where a designated product, process or method is expected to be transferred
Spiking	The addition of a known amount of a compound to a standard, sample or placebo, typically for the purpose of confirming the performance of an analytical procedure
Standard operating procedure (SOP)	An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (e.g., equipment operation, maintenance and cleaning, validation, cleaning of premises and environmental control, sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch Production documentation.
Technology transfer report	A documented summary of a specific technology transfer project listing Procedures, acceptance criteria, results achieved and conclusions. Any deviation should be discussed and justified
Validation	Action of proving and documenting that any process, procedure or method actually, and consistently leads to the expected results
Validation master plan (VMP)	A high-level document that establishes an umbrella validation plan for the entire project and summarizes the manufacturers overall philosophy and approach, to be used for establishing performance adequacy. It provides information on the manufacturer's validation work programme and defines details of and timescales for the validation work to be performed, including a statement of the responsibilities of those implementing the plan.
Validation protocol (or plan) (VP)	A document describing the activities to be performed in a validation, including the acceptance criteria for the approval of a manufacturing process — or a part thereof — for routine use
Validation report (VR)	A document in which the records, results and evaluation of a completed Validation programme are assembled and summarized. It may also contain Proposals for the improvement of processes and or equipment.

5 Responsibilities

For Technology Transfer of New Products (From R&D to Plant) :

Sr. No.	Function / Department	Responsibility
1	Formulation Development Department (FDD)	❖ To share Master Formula Card & other details as per Annexure 1 & 2 to the plant team.
2	Analytical Development Department (ADD)	❖ To share Materials, reagents & Products specification & protocols, other details required for Analytical Method Transfer as per Annexure -1
3	Packaging Development Department (PDD)	❖ To share Master Packaging Card & other details related to packaging process as per Annexure -1
4	Manufacturing Science & Technology (MS&T)	❖ To review all the documents provided by R&D. ❖ To prepare the documents required for Scale up (SU) / Exhibit batches (EB) initiation at site. ❖ To co-ordinate with all the cross functional team for smooth transfer of technology
5	Manufacturing	❖ To review the SU/EB documents & support for the manufacturing of the batches
6	Quality Assurance	❖ To review / authorize all the documents ❖ To Prepare protocols & conduct the studies as per requirement
7	Quality Control	❖ To perform the analytical method, transfer & sample analysis of SU, EB batches
8	Regulatory Affairs	❖ To review the Data/documents & support for regulatory filling

For Site Transfer Products:

Sr. No.	Function / Department	Responsibility
9	Manufacturing Science & Technology (MS&T)	❖ To review of Sending Site Document & absorb the technology from Sending site to scale it up at plant with support from Cross functional teams ❖ Responsible for Execution of Characterization / Feasibility studies/ exhibit batches / Pre-validation and Process validation studies as applicable.
10	Plant Head or designee (Sending Unit)	❖ The manufacturing location from where the product is to be shifted is responsible for providing the site transfer dossier to the proposed manufacturing locations
11	Plant Head or designee (Receiving Unit)	❖ Responsible for receiving the site transfer dossier from the donor site in case of site transfer products and allocation for evaluation by respective function.
12	Planning /Project Management/ Purchase	❖ Responsible for scheduling manufacturing and packaging of the batches. ❖ Procure and ensure that the required raw materials/ packaging material are available as per the request for the Scale-up / Exhibit / Process Validation Batches as per schedule.
13	Regulatory Affairs	❖ Responsible to ensure applicable license availability ❖ Regulatory filing of the exhibit batches for Technology transfer.
14	Manufacturing	❖ Responsible for evaluation of site transfer products w.r.t evaluation of manufacturing process, equipment details, batch size, change parts procurement. ❖ Execute Scale-up and Exhibit Batches in collaboration with MS&T and documentation thereof.
15	Quality Control	❖ To ensure availability of approved specifications and analytical test procedure for Drug Substance / Raw Material / Packaging Material and to ensure their testing and release for the scale up and exhibit batch execution. ❖ Ensure availability of analytical method transfer activity for API and Drug Product. ❖ Test scale up batches & exhibit batches samples
16	Quality Assurance	❖ Review and approve technology transfer documents for accuracy, completeness and correct transcription of information. ❖ Review and approve any other document/report such as cleaning method development/ validation protocol and report/ temperature excursion study protocol and report, if being performed at other site as per existing site-specific procedure
17	Engineering	❖ To ensure availability of requisite utilities and Equipment's

12 Process Design

- The Technology Transfer is divided into different phases:
  - Evaluation and decision phase
  - Planning phase
  - Preparation phase
  - Execution phase
  - Assessment phase
  - Closure and Post-transfer phase

Phases of Technology Transfer

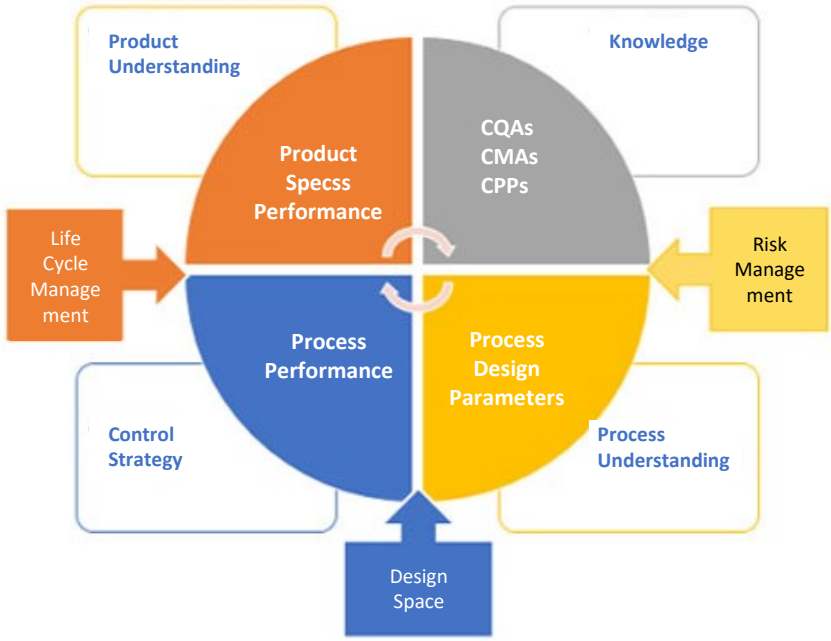
- The Technology Transfer is described in this Guidance as a sequence of activities. Some of the activities can in principle be performed in parallel or different order, if agreed by both, SU and RU. This should only happen, if appropriate, reasonable and justified. However, the revising of activities should be in general accordance with the overall concept described in this Guidance.
- The foundation of robust product starts with Pharmaceutical product development as per ICH Q8(R2). Better understanding of product at development stage may assist in technology transfer.
- A more systematic approach to development (also defined as quality by design) can include, for example, incorporation of prior knowledge, results of studies using design of experiments, use of quality risk management, and use of knowledge management (see ICH Q10) throughout the lifecycle of the product.
- A greater understanding of the product and its manufacturing process can create a basis for more flexible regulatory approaches during technology transfer and during product lifecycle.
- The degree of regulatory flexibility is predicated on the level of relevant scientific knowledge provided in the registration application. It is the knowledge gained and submitted to the authorities, and not the volume of data collected, that forms the basis for science- and risk-based submissions and regulatory evaluations.
- Following are the steps in pharmaceutical product development by Quality by Design (QbD) approach as per ICH Q8(R2):

QTPP **Quality Target Product Profile**	❖The quality target product profile forms the basis of design for the development of the product. ❖It includes (not limited too) Dosage strength, container closure system, pharmacokinetics characteristics and quality criteria like purity, stability, sterility, drug release)
CQA **Critical Quality Attributes**	❖A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. ❖CQAs are generally associated with the drug substance, excipients, intermediates, in-process materials) and drug product
Risk Assessment for CMA & CPP	❖Identifying which material attributes and process parameters potentially have an effect on product CQAs by Risk assessment (science-based process) used in quality risk management (see ICH Q9)
DOE **Design of Experiment**	❖Experimental designs are the systematic multivariate tools for optimisation of the drug products and processes using minimum experimentation to unearth maximal outcome. ❖ DOE study is used to define the range or limit of material attributes, composition, unit operation, Scale & equipment which yield consistent desirable results.
Design Space	❖Design space (also referred as proven acceptable range) is a multidimensional combination of relationship between the CMAs/CPPs. When design space is established between CMAs and CQAs, then it is considered as product design space, while design space established between CPPs and CQAs is referred as process design space
Control Strategy	❖A control strategy is designed to ensure that a product of required quality will be produced consistently. ❖Control strategy can justify how in-process/Finished controls and controls of input materials (drug substance and excipients), intermediates (in-process materials), container closure system, and drug products contribute to the final product quality.
ICH Q10 **Product Lifecycle Management and Continual Improvement**	❖Process performance can be monitored to ensure that it is working as anticipated to deliver product quality attributes as predicted by the design space. ❖Expansion, reduction or redefinition of the design space could be desired upon gaining additional process knowledge. Change of design space is subject to regional requirements.

Similar approach is applicable to Analytical QbD. Step involved in Analytical QbD is as follow:

ATP **Analytical Target Profile**	❖ATP is an analogue to QTPP. ATP defines the goal of the analytical method development process, relating the results of the method to achieve QTPP. ❖ATP identification includes the selection of method requirements such as target analytes (product and impurities), analytical technique category, and product specifications.
CQA **Critical Quality Attributes**	❖CQA for analytical methods includes method attributes and method parameters. Each analytical technique has different CQA. HPLC (UV or RID) CQA are mobile phase buffer, pH, diluent, column selection, organic modifier, and elution method. GC methods CQA are gas flow, oven temperature and program, injection temperature, sample diluent, and concentration. Similarly it may differ with analytical method.
Risk Assessment	❖Risk Assessment is a science-based process used in quality risk management and it can identify the material attributes and method parameters (ATP)
DOE: Design of Experiment (Method Optimization and Development)	❖Once the potential and critical analytical method variables are defined with initial risk assessment, then DoE can be performed to confirm and refine critical method variables based on statistical significance. It can be determined per unit operation or combination of selected multiple method variables and their interactions and responses (critical method attributes).
MODR (Method Operable Design Region)	❖Method operable design region (MODR) is used for establishment of a multidimensional space based on method factors and settings; MODR can provide suitable method performance. It is also used to establish meaningful method controls such as system suitability, RRT, and RRF. Further method verification exercises can be employed to establish ATP conformance and ultimately define the MODR.
Control Strategy	❖Control strategy is a planned set of controls, derived from analyte nature and MODR understanding. Method control strategy can be established based on the complete statistical data collected during the DoE and MODR stages. Control strategy will resolve the method parameters inconsistency (e.g., reagent grade, instrument brand or type, and column type).
ICH Q14 **Analytical Procedure Lifecycle Management**	❖Continuous Method monitoring (CMM) is final step in AQbD life cycle; it is a continuous process of sharing knowledge gained during development and implementation of design space. This includes results of risk assessments, assumptions based on prior knowledge, statistical design considerations, and bridge between the design space, MODR, control strategy, CQA, and ATP.

- Interlinking of ICH Q8(R2) – Pharmaceutical Development, ICH(Q9) Quality Risk Management and ICH Q10 – Pharmaceutical Quality System is pictorially shown Figure -1:

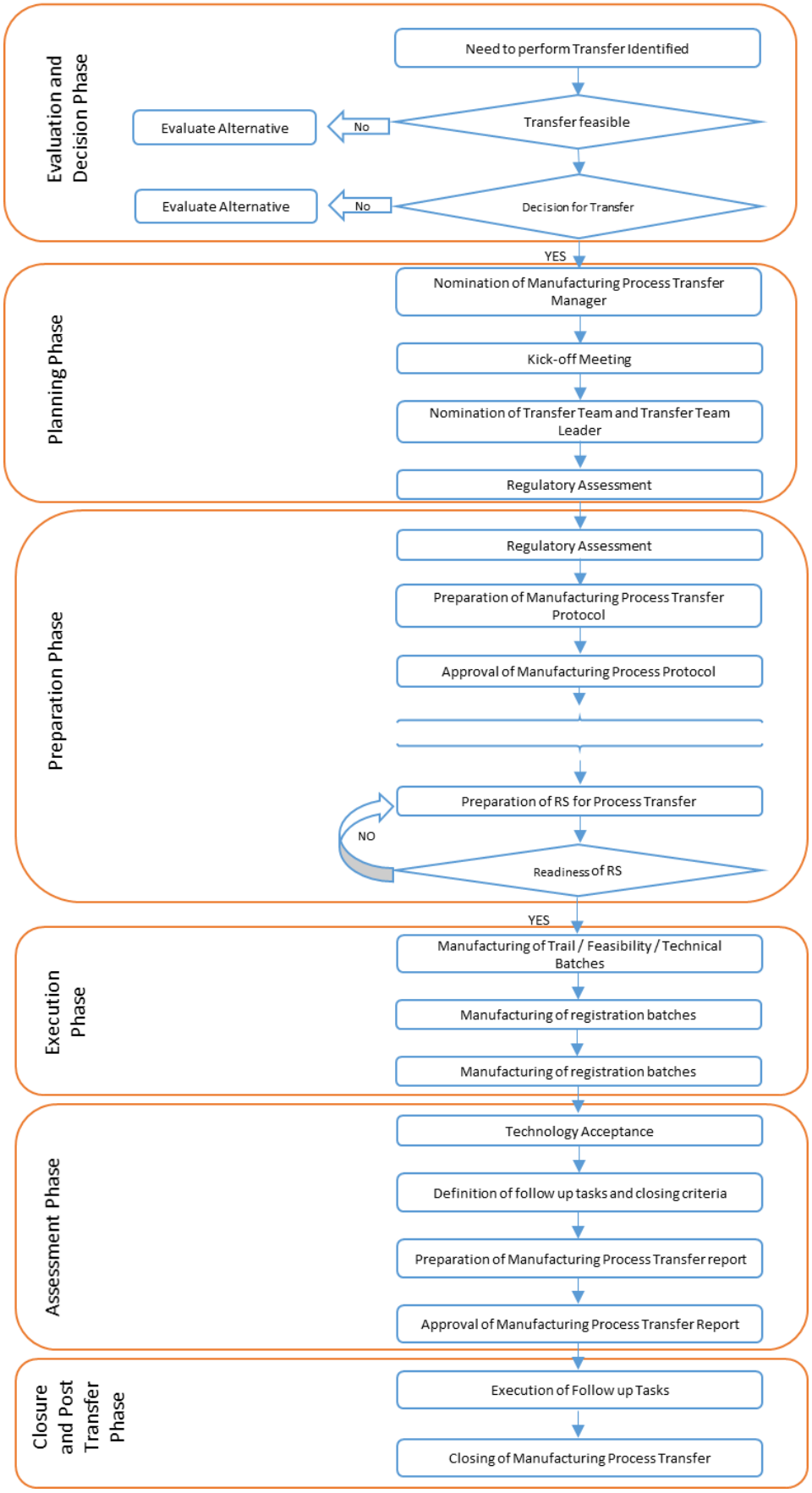


- After successful completion of product Development phase ICH Q8, next phase is Process validation.
- As per ICH Q10, Process Validation Lifecycle Approach are categorised in 3 phases-
  - Stage I: Process Design
  - Stage II: Process Qualification
  - Stage III: Continuous Verification
- If we correlate the different technology transfer phases with ICH Q10 as above, it can be further categorised as below-

ICH Q10-Stages of Product Lifecycle	Technology Transfer Phases
Stage I: Process Design	1. Evaluation and decision phase
	2. Planning phase
	3. Preparation phase
Stage II: Process Qualification	4. Execution phase
	5. Assessment phase
Stage III: Continuous Verification	6. Post-transfer phase

- Product transfers most often involve two components: Manufacturing Process Transfer and Analytical Method Transfer.
- All efforts should be made to ensure that the process and method transfer activities are coordinated and aligned to ensure that the technology transfer will be successful.
- The Manufacturing Process Transfer is a sequence of phases. Changes in terminology and combinations of activities of different phases into fewer steps are justified. Some of the activities can in principle be performed in parallel or different order, if agreed by both SU and RU. However, applicable basic elements as described hereafter shall be covered in their entirety.

❖ The flow chart of the overall process of a Technology Transfer is depicted in Figure 2.



13 Procedure

❖ **STEPS INVOLVED IN TECHNOLOGY TRANSFER PROCESS**

❖ During development of a formulation, it is important to understand the procedure of operations used, critical and non-critical parameters of each operation, production environment, equipment and excipient availability should be taken into account during the early phases of development of formulation.

(A) Development of technology by R&D. (Research Phase)

(a) Design of procedure and selection of excipients by R&D – Selection of materials and design of procedures is developed by R&D on the basis of innovator product characteristics.

(b) Identification of specifications and quality by R&D – Quality of product should meet the specifications of an innovator product.

(B) Technology transfer from R&D to production (Development Phase)

❖ R&D provides technology transfer dossier (TTD) document to product development laboratory, which contains all information of formulation and drug product as follows –

(a) Master Formula Card (MFC) – Includes product name along with its strength, generic name, MFC number, page number, effective date, shelf life and market.

(b) Master Packing Card – Gives information about packaging type, material used for packaging, stability profile and shelf life of packaging.

(c) Master Formula – Describes formulation order and manufacturing instructions. (Process order and environment conditions.

(d) Specifications and Standard Test Procedures (STP'S) – Helps to know active ingredients and excipients profile, in-process parameters, product release specifications and finished product details.

(C) Optimization and Production. (Production Phase)

(a) Validation Studies – Production is implemented after validation studies that can verify that process is able to stabilize the product based on transferred manufacturing formula. Manufacturing department accepting technology is responsible for validation and the R&D department transferring technology should take responsibility for validation such as performance qualification, cleaning and process validation.

(b) Scale up for production – Involves the transfer of technology during small scale development of the product and processes. It is essential to consider the production environment and system during development of process. Operators should concentrate on keeping their segment of the production process running smoothly.

(D) Technology Transfer Documentation –

❖ Generally interpreted as document indicating contents of technology transfer for transferring and transferred parties. Each step from R&D to production should be documented, task assignments and responsibilities should be clarified and acceptance criteria for completion of technology transfer concerning individual technology to be transferred. It is duty of Quality Assurance department to check and approve the documentation for all processes of technology transfer.

(a) Development Report – The R&D report is a file of technical development, and R&D department is in-charge of its documentation. This report is an important file to indicate rationale for the quality design of drug substances and its specifications and test methods. The development report is not prerequisite for the application for approval; it can be used at the pre-approval an inspection as valid document for quality design of new drug. The development report contains –

(1) Data of pharmaceutical development of new drug substances and drug products at stages from early development phase to final application of approval.
(2) Information of raw materials and components.
(3) Design of manufacturing methods.
(4) Change in histories of important processes and control parameters.
(5) Specifications and test methods of drug substances.
(6) Validity of specification range of important tests such as contents impurities and dissolution.
(7) Verifications of results.

(b) Technology Transfer Plan – The technology transfer plan is to describe items and contents of technology to be transferred and detailed procedures of individual transfer and transfer schedule, establish judgment criteria for the completion of the transfer. The transferring party should prepare the plan before the implementation of the transfer and reach an agreement on its contents with the transferred party.

(c) Report – Completion of technology transfer is to be made once data are taken accordingly to the technology plan and are evaluated to confirm that the predetermined judgment criteria are met. Both transferring and transferred parties should document the technology transfer report.

(E) Exhibit –

❖ After taking scale up batches of the product, manufacturing of exhibit batches takes place. In case of exhibit, batch sizes are increased along with equipment and their processes. This is done for filling purpose in regulatory agencies.

(F) Packaging of Exhibit Batches-

- As per applicable regulatory and scientific requirement one complete exhibit batch will be fully packaged in all marketable packaging configurations.

- Representative samples from the remaining two exhibit batches must be packaged in a sufficient number of proposed marketing presentations which may be ¼ th of the batch that can be packaged into marketable pack configuration or as per requirement.

- Stability bracketing and/or matrixing may be used to determine the packaging configurations to be charged on stability studies.

- Procedure for technology transfer activity shall be followed as per the flow mentioned above

- **For Registration purpose: Technology Transfer from Development Lab to Manufacturing Unit of-Own site or CMO site**

1. Evaluation and decision phase

- Transfer of technology requires a documented, planned approach using trained and knowledgeable personnel working within a quality system, with documentation of data covering all aspects of development, production and quality control. Usually there is a sending unit (SU), a receiving unit and the unit managing the process, which may or may not be a separate entity.
- For New product, Development lab should develop the product considering QbD approach for formulation, analytical and process and as per current regulatory expectations for respective dosage form.
- The batch with final formula/ process shall be the one for which qualitative and quantitative formula is finalized based on product development study.
- Development centre shall finalize the submission batch size and equipment along with Supply chain, Regulatory & site Manufacturing Science & Transfer group based on tentative manufacturing process flow, tentative commercial volume, and criticality of manufacturing process, equipment availability at receiving site.
- For commercial products/Legacy products, Supply chain shall identify and initiate site shift activity of product to be transferred in consultation with all relevant cross functional teams based on plant capacity, business strategy, regulatory requirement etc.
- Technology transfer projects, particularly those between different companies, have legal and economic implications. If such issues, which may include intellectual property rights, royalties, pricing, conflict of interest and confidentiality, are expected to impact on open communication of technical matters in any way, they should be addressed before and during planning and execution of the transfer.

2. Planning Phase

- After finalising the receiving unit and batch size, Nomination of Technology transfer team members shall be proposed by Development centre/CMO/SU.
- The team member should include as below (Not limited to)
    - Manufacturing/Production
    - Logistics/ Supply chain
    - Engineering
    - Manufacturing science and technology group/process development group
    - Quality unit/ quality control/ quality assurance
    - Health, safety and environment
    - Regulatory affairs
    - Member of the transfer team of the analytical method transfer
    - Research scientist
- The RU should be able to accommodate the intended production capacity. If possible, it should be established at the outset whether the intention is to perform single-batch manufacture, continuous production or campaigns.

3. Preparation Phase

- Consideration should be given to the level and depth of detail to be transferred to support production and any further process development and optimization at the RU as intended under the transfer project plan.
- Consideration should be given to the technical expertise, site technology and site capabilities for the RU. It should be identified upfront by the SU of any process robustness issues so that plans may be put in place for risk mitigation at the RU.
- All relevant information needs to be shared by development centre with receiving unit like (not limited to), CMAs, unit operation wise CPPs, quality attribute and other process parameter, CQA, challenge study data, CMAs impact assessment on CQAs, CPPs impact assessment on CQAs, residual risk after development and control strategy (process parameters, material specifications, unit operation wise testing and sampling plan with rational), stability data and manufacturing details.
- Development Centre shall prepare equipment equivalency and scale up correlation report along with rational and justification based on scale up factors (as per applicability) and shall propose process parameter in respective protocol / BMR.
- Based upon knowledge gained during product development, QbD trials scale up report and other development studies, Development centre shall finalize the PDR, Product Specification and stability study proposal.
- PDR shall become the base document for further finalisation of MFC and In-process sampling protocol with details of scale dependent and scale independent parameters.
- The material attributes, process parameter and quality attributes for each unit operation which should be taken into consideration during technology transfer are mentioned in Annexure - III.

- Development centre-Packaging development department shall also share separate sampling plan for packed batches which includes unit dose primary packing (e. g. HDPE bottles, Sachet, Tube filling, Blisters etc).
- Development centre shall evaluate applicable PAT application and complete PAT development activity with before initiation of technology transfer activity.
- Risk assessment with the involvement of all CFTs like-formulation development, analytical development, Manufacturing Science & Technology, packaging development, Quality Assurance, Engineering (not limited to) shall perform to identify required controls, which needs to be addressed in relevant document.
- This risk assessment shall address the unit operation wise critical process parameters/ non critical process parameter, which may have direct and /or indirect impact on manufacturing process as well as on product quality.
- Based on the residual risk, the risk mitigation plan and control strategy shall be evaluated or established.

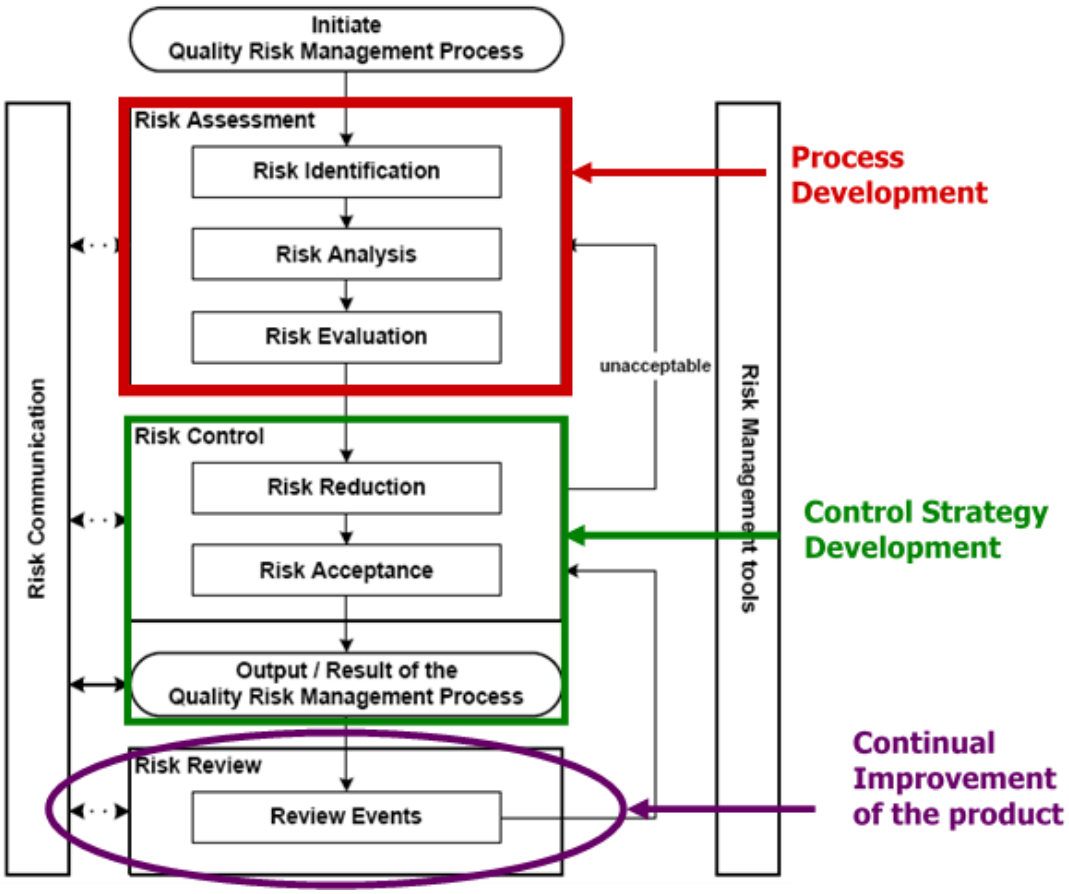


Figure 4 - Overview of a typical quality risk management process

Knowledge Sharing

- The Scale Up should provide a detailed characterization of the product, including its qualitative and quantitative composition, physical description, method of manufacture, in-process controls, control method and specifications, packaging components and configurations, and any safety and handling considerations. It should also include product robustness assessment on final formula proposed.

- All relevant departments of development centre / CMO as mentioned in technology transfer team shall share the detailed Product development knowledge with the concerned departments of receiving unit.

- This knowledge sharing session and respective presentation shall contain following information (but not limited to):
    - Description of chemistry, physical chemistry and biology involved in the process as well as innovator characterisation.
    - Summary of knowledge gained from development batches
    - Information on scale-up activities: process optimization, statistical optimization of critical process parameters, critical quality attributes, pilot bio study report and or information on pilot-scale development activities indicating the number and disposition of batches manufactured
    - Information or report on full-scale development activities, indicating the number and disposition of batches manufactured, and deviation and change control (sometimes referred to as change management) reports which led to the current manufacturing process;
    - Unit operation wise CPP, other process parameter
    - CMAs, CQAs and impact of unit operations on CQAs, control strategy and recommendations
    - Potential sources of variation
    - The SU should provide to the RU information on any health, safety and environmental issues associated with the manufacturing processes to be transferred, and the implications, e.g., need for gowning or protective clothing.
    - Quality assurance department of receiving unit shall maintain records of knowledge sharing session (including presentation copy and MOM) along with technology transfer documents.
    - The change history and reasons, e.g., a change control log, indicating any changes to the process or primary packaging or analytical methods as a part of process optimization or improvement.
    - Information on investigations of problems and the outcomes of the investigations.
    - Refer Annexure -1 for content of knowledge sharing (not limited to)

Document Transfer

- Technology Documents Transfer — Formulation:
  - The technology transfer documents as per Attachment-II shall be prepared, and approved as per respective SOP by relevant departments. Controlled copies of listed documents shall be distributed through CQA document cell to respective manufacturing site QA before execution of batch (es).
  - List of Documents (Not limited to) as summarised below shall be transferred to RU.
    1. Information on starting materials, applicable MSDS and storage requirements for raw materials and finished products
    2. Formulation Process Evaluation
    3. RM/PM specification and Standard test procedure: RM, PM, In process, Intermediate, Semi-finished, Finished, Shelf life stage
    4. Description of analytical methods
    5. Method Validation report
    6. Method of analysis for dissolution profile (wherever applicable)
    7. Risk assessment form(s)
    8. Identification and justification of control strategy (e.g., identification of critical performance aspects for specific dosage forms, identification of process control points, product quality attributes and qualification of critical processing parameter ranges, statistical process control (SPC) charts)
    9. MFC and MPD
    10. PAT related documents
    11. Information Sheet for Stability/Transit/In Use/Freeze thaw Stability Protocol preparation
    12. In process sampling protocol (for Manufacturing & Primary unit dose packing) and Finished Product sampling protocol
    13. Analytical Method Transfer Protocol, Data sheet, report
    14. Product Development Report (PDR) and Packaging Development Report
    15. Design space, in cases where this has been defined
    16. Annual product quality reviews;

Technology Transfer— Analytical Method:

- Analytical methods used to test pharmaceutical products, starting materials, packaging components and cleaning (residue) samples, if applicable, should be implemented at the testing laboratory before testing of samples for process validation studies is performed by the RU. Process validation samples may be tested at the RU, the SU or a third-party laboratory.

- A protocol defining the steps should be prepared for transfer of analytical methods. The analytical methods transfer protocol should include a description of the objective, scope and responsibilities of the SU and the RU; a specification of materials and methods; the experimental design and acceptance criteria; documentation (including information to be supplied with the results, and report forms to be used, if any); procedure for the handling of deviations; references; signed approval; and details of reference samples (starting materials, intermediates and finished products).

- The SU's responsibilities for the transfer of analytical methods are to:
    - provide method-specific training for analysts and other quality control staff, if required;
    - Assist in analysis of QC testing results;
    - Define all methods to be transferred for testing a given product, starting material or cleaning sample;
    - Define experimental design, sampling methods and acceptance criteria;
    - Provide any validation reports for methods under transfer and demonstrate their robustness;
    - Provide details of the equipment used, as necessary (part of validation report, if available) and any standard reference samples;
    - Provide approved procedures used in testing;
    - Review and approve transfer reports

The RU's responsibilities are to:

- Review analytical methods provided by the SU, and formally agree on acceptance criteria before execution of the transfer protocol;
- Ensure that the necessary equipment for QC is available and qualified at the RU site. The equipment used by the RU during the analytical transfer should meet appropriate specifications to ensure the requirements of the method or specification are met;
- Ensure that adequately trained and experienced personnel are in place for analytical testing;
- Provide a documentation system capable of recording receipt and testing of samples to the required specification using approved test methods, and of reporting, recording and collating data and designation of status (approved, rejected, quarantine);
- Execute the method transfer protocol;
- Perform the appropriate level of validation to support the implementation of the methods; and
- Generate and obtain approval of transfer reports.

- It is recommended to perform the demonstration of analytical methods by SU-QC to RU-QC and based on mutual agreement, Standard testing procedure shall be prepared for a method validation/ verification (as applicable) study by RU QC.

- Sending Unit (Development centre/CMOs) shall transfer Analytical method to receiving unit in concurrence to relevant regulatory guideline and GxP aspects

- Possible experimental designs and acceptance criteria for the main analytical testing methods are shown in Table 1. Note that this table represents high-level guidance to apply the general principle that method transfers should account for the variability and sensitivity of the method and the specifications for the quality parameter. Alternative procedures and acceptance criteria may be applied based on science and the characteristics of the analytical method and the analyte.

Possible experimental designs and acceptance criteria for analytical testing

Test	Considerations for transfer	Replication of tests	Set-up	Acceptance criteria	
				Direct	Statistically derived
Identity	Transfer should focus on sample preparation, instruments, data interpretation. Acceptable to include in assay transfer where relevant	One determination usually sufficient to demonstrate equivalence			
Assay for potency	– *Non-specific assay should not be used for stability testing.* – Bracketing may be appropriate for multiple strengths	At each site: 2 analysts × 3 lots, in triplicate (= 18 per site)	Different sets of instruments and columns Independent solution preparation	Comparison of mean and variability	Two one-sided *t*-tests with intersite differences ≤ 2% , 95% confidence
Content uniformity	If method is equivalent to assay method, separate transfer is not usually requird	At each site: 2 analysts, × 1 lot (= 2 per site)	Different sets of instruments and columns Independent solution preparation	Mean at RU within ± 3% of mean at SU; comparison of relative st. dev.	Two one-sided *t*-tests with intersite differences ≤ 3% , 95% confidence
Dissolution	Bracketing may be appropriate for multiple strengths	6 units (12 if not routine at RU, and for extended release products)		Mean at RU within ± 5% of mean at SU	Compare profile (e.g. F^2), or Compare data at Q time points as for assay
Cleaning verification (recovery of residues from surfaces)	Confirm that same swabbing material is used at sending unit (SU) and receiving unit (RU)		Use spiked samples, with levels within 3× validated st. dev. or within ± 10% of specification (whichever is the greater)	– All samples spiked above specification should fail – 90% of samples spiked below specification should pass	
Microbiological testing (qualitative and quantitative limit tests)	– Execute common on-site validation protocol: rationale; method identity; validation parameters; data summary; acceptance criteria; methods of compiling and analysing data; handling of out-of-specification results; follow-up requirements – Use same materials, techniques, inoculum preparation	Validation in triplicate	Use different lots for each validation exercise	– Qualitative: Demonstrate recovery of microorganisms – Quantitative: Recovery levels within acceptance limits specified in protocol	
Impurity, degradation, residual solvents	– Confirm response factors for calculation relative to drug peak; – Confirm limit of quantitation at RU; – Compare chromatograms – Compare accuracy and precision for spiking experiments	At each site: 2 analysts × 3 lots, in duplicate (in triplicate if done together with assay)	– Different days, different sets of instruments and columns – Use samples of similar age, homogeneity, packaging, storage – Use spiked samples if necessary	(For low levels) Values at RU within ± 25% of values at SU, or Mean at RU within ± 0.05% of mean at SU (5%)	(For moderately high levels) Two one-sided *t*-tests, differences ≤ 10%, 95% confidence

st. dev., standard deviation.
Note: numbers in the table are given as examples only and should not be considered as recommendations.

- The SU and the RU should execute the transfer protocol and jointly prepare a transfer report. The points to be addressed in the analytical methods transfer report are listed in these guidelines.

- Cleaning procedures and their validation are site-specific. In order for the RU to define its cleaning strategy the SU should provide information on cleaning at the SU to minimize cross-contamination due to residues from previous manufacturing steps, operator exposure and environmental impact, including:
    - Information on solubility of active ingredients, excipients and vehicles;
    - Minimum therapeutic doses of active ingredients;
    - Therapeutic category and toxicological assessment; and
    - Existing cleaning procedures.
    - Cleaning validation reports (chemical and microbiological);
    - Information on cleaning agents used (efficacy, evidence that they do not interfere with analytical testing for residues of APIs, removal of residual cleaning agents)
    - Recovery studies to validate the sampling methodology.

- During the transfer process, the RU should identify any differences in facilities, systems and capabilities and communicate with the SU about these differences to understand the potential impact on ability to run the process to deliver good product quality. Differences should be understood and satisfactorily addressed to assure equivalent product quality. Based on the information received from the SU, the RU should consider its own capability to manufacture and pack the product to the required standards and should develop relevant plant operating procedures and documentation before the start of production

- Based on review of all documents shared from SU, RU will initiate the document preparation for new product batch execution as per the respective SOPs of the RU.

- Reference Annexure-II for Exhibit batch initiation checklist.

4. Execution Phase

Exhibit batches:

- After ensuring availability of required facilities, approved documents, approved raw materials and manufacturing license, RU shall plan for manufacturing of batch(s) with confirmation from other relevant departments.

- Trial batch(es) (“demonstration batches”) are normally produced to confirm process capability before initiating formal validation. For new products which are developed by R & D, initial trial batches made at R & D along with technology transfer group to understand and check reproducibility. This also helps to transfer knowledge between R & D scientist and technology transfer personnel. After this trial batches are produced at plant level, all critical processing parameters and finished product specifications should be assessed.

- Trial/engineering batches can be exempted based on scientific justification e.g., Scaleup factor application in scale change, with risk management. Factors which can be considered during scale up factor application are mentioned in Annexure III.

- If required, engineering batch can also be executed before executing the submission batch for process optimization.

- Once process capability has been established at the RU, assuring that the product, process or method at the RU meets predefined and justified specifications, exhibit cum process validation batches and cleaning validation can be carried out.

- To understand the commercial process sufficiently, the manufacturer will need to consider the effects of scale. However, it is not typically necessary to explore the entire operating range at commercial scale if assurance can be provided by process design data

- These batches will have a higher level of sampling, additional testing, and greater scrutiny of process performance as compared to routine commercial production. The level of monitoring and testing should be sufficient to confirm uniform product quality throughout the batch. Considerations for the duration of the heightened sampling and monitoring period could include, but are not limited to, volume of production, process complexity, level of process understanding, and experience with similar products and processes.

- In the event that the RU identifies particular problems with the process during the transfer, the RU should communicate them back to the SU to ensure continuing knowledge management.

- Based on the successful completion of exhibit batches, recommendation for process parameter to be added or updated for existing parameters for process validation batches.

- For different batch size process parameter recommendation to be given based on batch size and equipment (Scale dependant & Scale independent parameters as per annexure III).

- Stability trend data of Exhibit batches at different stability conditions to be critically monitor for any shift in mean or sudden increase or decrease beyond trend. Such change shall be compared to developmental batches data and if required data to be investigated.

5. Assessment Phase

- If any changes are suggested from the outcome of Engineering batch/submission batch(s)/ learning from submission batches, then RU shall inform to SU to initiate the revision of relevant documents as per requirement such as PDR, MFC, specifications, STP (not limited to), based on proposal from RU.

- SU and RU shall ensure that process evaluation of submission batches are completed, concluded and the batches are subjected to stability studies

- Submission batch summary report shall be prepared by RU and reviewed by SU and other cross functional team.

- Any residual risk along with control strategy is to be address in batch summary report of submission for future batches.

- After filing, if any change(s) suggested by regulatory agency viz. Process parameter, design space, specification or any technology transfer documents, then a change control shall be initiated by concern department for the proposed change and as per category and impact assessment of change risk assessment shall be done by cross function team prior to change in documents.

Validation Cum commercial batches:

- Product launch decided based on regulatory approval & patent expiry time line.

- Batch size of product decided based on commercial volume, equipment capacities & respective regulatory guidance etc.

- All queries and response after filing need to be reviewed and difference in specification if updated need to be evaluated. Based on this if any risk which arises need to be evaluated and mitigation strategy to be decide.

- For any change in batch size compared to exhibit batches, equipment capacities, occupancy, similarity of equipment's to be evaluated.

- Characterisation batch/pre validation batch need to be planned to optimise process parameter due to change in batch size/equipment's.

- Real hold time batch to be planned well in advance to justify proposed hold time mentioned in BMR. This should be done by holding each stage sequentially before carrying out next operation. Real hold time batch should be loaded to stability and same need to be monitored till shelf life.

    - In general, the in process stages to be considered for the subject study for various dosage forms are as under, but not limited to :

Blend Stage	After Sifting/ Milling, Wet milling, Drying, Dry sifting & Milling
Tablets	In process bulk blend, core and / or uncoated/film coated/sugar coated/enteric coated tablets before primary packaging.
Hard Gelatin Capsules	In-Process bulk blends and filled capsules before primary packaging.
Soft Gelatin Capsules	In-Process bulk blends and filled capsules before primary packaging.

    - Risk assessment to determine the requirement for performing hold time study, testing time points, testing requirements, etc. shall be performed and documented in In process Hold time (IPHT) protocol. Hold Time study shall be performed on one batch or more based on risk assessment and regulatory requirement.

- The hold time studies can be performed at various stages of a drug product lifecycle (as applicable) like Process development/Scale up batch or Test/Exhibit or Characterization / Pre-validation / Process Validation batch or PPQ batches or Commercial batches (at manufacturing site).

- Real Hold Time Study: Real hold time study shall be performed on an entire batch (or multiple batches). Characterization or Engineering batch can be prepared for hold time study. The entire batch is subjected to the hold time e.g. if the stage hold time is 15 days, the entire batch is subjected to 15 days' 'hold' with subsequent stage processing only after the stipulated hold time period of respective manufacturing stage has elapsed.

- Following precaution to be taken, if separate batch is prepared.
    - All RM shall be same as per the approved product
    - Manufacturing process shall be same as per approved product.
    - All equivalent equipment shall be used in line with those used in approved product.
    - During the hold time study, the entire batch being manufactured, shall be processed in sequence by holding the complete batch at different in-process stages of product in actual simulated condition, as those of the quarantine area / manufacturing stage.
    - Hold time study shall be performed on approved manufacturing instruction of the drug product, where commercial batch is used for IPHT study and study time frame of hold period shall be referred from the respective IPHT protocol. The batch shall be kept in the storage containers provisioned to be used during routine commercial batch manufacturing.
    - Batches shall be charged on accelerated and long term condition stability condition and based on satisfactory results of 03 months accelerated stability data, commercial hold time study batch can be released to market after statistical evaluation and regulatory acceptance.

- For process validation of new product mainly two type of validation approaches are considered – prospective validation (For three batches) or concurrent validation (For One batch at a time).

- Concurrent validation to be used for certain category of drugs like orphan drug, low demand, short shelf life (radioactive). Conclusions about a commercial manufacturing process can only be made after the PPQ protocol is fully executed and the data are fully evaluated. If Stage 2 qualification is not successful (i.e., does not demonstrate that the process as designed is capable of reproducible performance at commercial scale), then additional design studies and qualification may be necessary.

- It is important to draw up a summarized document that describes the whole project. It has become common practice in the industry to develop a "validation master plan" (VMP). This document would usually include the qualification aspects of a project.

- After preparing VMP, the next step is to prepare validation protocol. There are the following contents in a validation protocol.

Sr. No.	Content
1	Protocol approval
2	Training Records
3	General information
4	Objective
5	Background/Prevalidation Activities Summary (Exhibit Batch Summary) of development and tech transfer (from R&D or another site) activities to justify in-process testing and controls; any previous validations.
6	Design and scope
7	List of equipment and their qualification status
8	Facilities qualification
9	Process flow chart
10	Risk Assessment Strategy and Approach
11	Evaluation of Formulation Ingredients (Comparison with Exhibit Batches)
12	Evaluation of Raw Material (Comparison with Exhibit Batches)
13	Evaluation of Equipment (Comparison with Exhibit Batches)
14	Manufacturing procedure narrative
15	List of critical processing parameters and critical excipients
16	Sampling, tests and specifications
17	Acceptance criteria
18	Deviation from Protocol

- Successfully validating a process may reduce the dependence upon intensive in-process and finished product testing.

- Country specific Scale up and Post approval guidance to be referred when any minor or major change is needed in formulation, Batch size, equipment, manufacturing process and process parameter during technology transfer (from exhibit to process validation). Refer Annexure-III for requirement of product launch checklist.

- Packaging validation to be critically performed as that of Drug product process validation.

- Packaging is interface between drug product and environment. Its purpose is to act as barrier and protect the drug product from external environment.

- The other purpose to sustain drug product in its original form without any damage, contamination and spoilage during transport of drug product from manufacturer to patient till the complete shelf life of the product

- Packaging process re-validation to be performed when there is change in source of material, material of packaging, change in packaging process & equipment or any support system

- Packaging Validation risk assessment shall be performed prior to packaging validation. Scope of packaging risk assessment can apply to equipment, process, process parameter, type of packaging (primary/secondary). Based on the risk

- Parameter considered for packaging validation may varies based on the type of Packaging for e.g. HDPE bottle (CRC and NCRC), blister packaging, Alu-Alu and others.

- Steps involve in blister and HDPE bottle Packaging are mentioned as below:

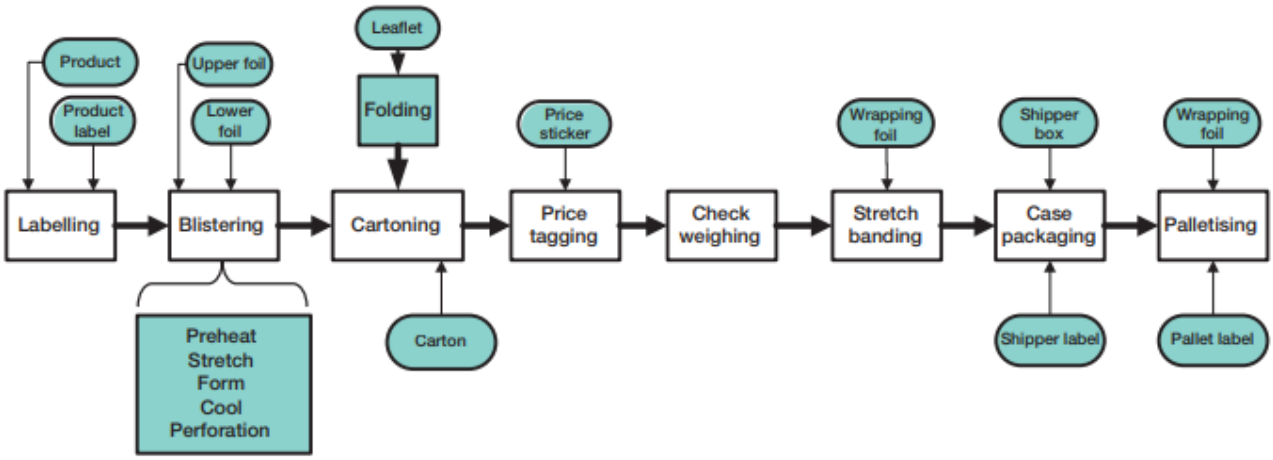


Figure- 5: Blister packaging line

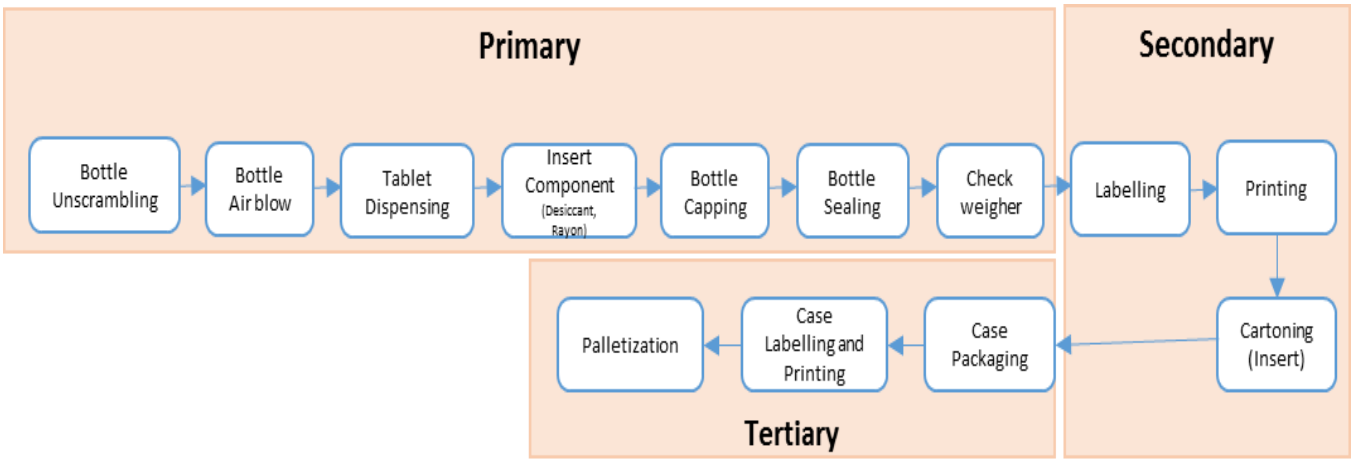
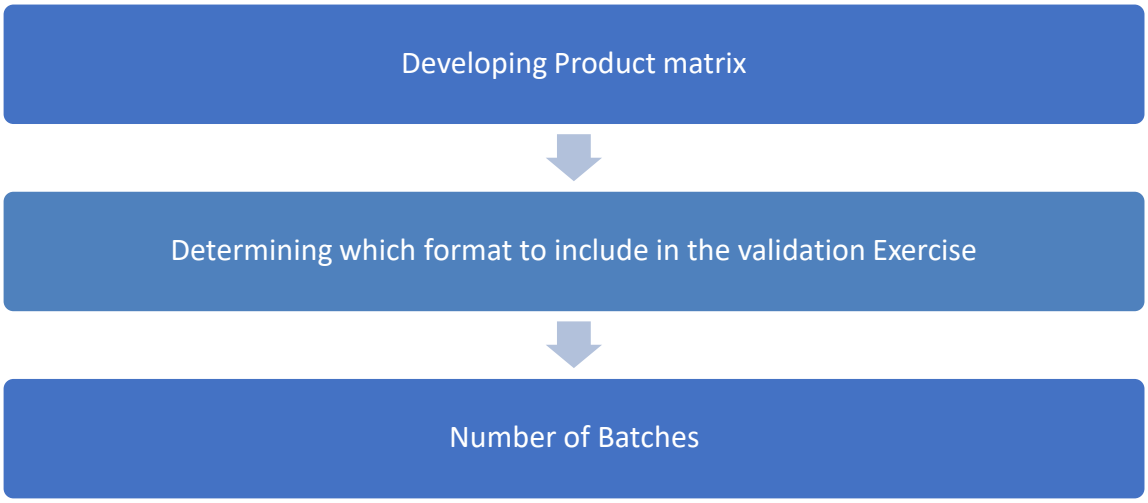


Figure-6: HDPE bottle packaging line

❖ Steps involve in Packaging Validation are mentioned in below flow chart:



❖ **Product Matrix:** Include the breadth of Product and Pack combination for e.g. Strength, type and size of bottle & Cap, count, presence of desiccant, speed, label.

❖ **Determine which format to be included in validation exercise:** A format is a combination of different drug/ package attributes, and equipment/process parameter that when combined, constitute a unique pack/process.

❖ **Number of Batches:** A risk analysis should be used to determine the number of batches required. Some of the factor which risk analysis should focus on include but not limited to; experience of understanding of product, process and equipment, control strategies adopted, complexity, impact to patient as evidence by impact to product and pack CQAs, level and length of PQ.

Approach to Process Validation of Packaging Process

❖ The Process Validation lifecycle for a Packaging Process shall be as follows:

Stage 1 (Process Design):

❖ The development / design studies of a new pack for a product may be divided into the following phases:

Phase	Important Activities
I	❖ Feasibility Studies, Development / design studies of new packs, Review of Product Information Form (if available), Literature search, Market search / Marketable pack requirements, Evaluation study of innovator/competitor packs
II	❖ Stability/Compatibility/Other Tests studies with various pack options, Risk Assessment and finalization of packaging configuration, preparation of Specification/STP, preparation of Packaging Development Report as per site SOPs ❖ Fitment assessment of packaging facility and equipment at the manufacturing site for the intended pack configuration, finalization of Packaging Change Parts/Machine/Line Setup, initiation of change part trials at manufacturing facility ❖ Qualification of Packaging Process / Optimization of Packaging Machine Process Parameters (PAR finalization), etc. on Scale-Up Batches and finalization of packaging process using Risk Assessment, trial results, etc., preparation of Packaging Process Design Summary Report ❖ Packing of stability batches*
III	❖ Conducting transit worthiness trials (if required) ❖ Finalization of pack design based on the above said studies ❖ Creation of artworks/mock-ups for regulatory submission, incorporation of texts on pack on the basis of compilation of product information including regulatory and marketing requirements and release for procurement, ❖ Verification of packaging process parameters during Exhibit Batches (EB)/Pre-Validation/Pre-PPQ batches and updation of the Packaging Process Design Summary Report, if needed
***This activity may be carried out using nearest fitting change part configuration of other products, etc. in case of exigencies; however, it is preferred that it be conducted post Packaging Process Qualification**	

❖ **Pre-Stage 2 of PV:**

- ❖ Qualified ranges of the process parameters, as finalized through the Packaging Process qualification activities shall be used during packaging of Exhibit Batches and Pre-Validation/Pre-PPQ Batches, as applicable.
- ❖ Rejections shall be monitored and recorded along with type of defects for the Exhibit Batches / Pre-Validation / Pre-PPQ. Major Rejection example for packaging are:
- ❖ **For blister rejection:** Leak test failure, Failure no fill detection (NFD) test, Abruptive feeding of tablets during blistering, Non uniform perforation and blister cutting, Wrong Batch coding etc.
- ❖ For bottle rejection: Tilted or loose cap, Unsealed cap, less or more Count, Leak test failure, Label smudging, Wrong Batch coding etc.

- The Packaging Process Design Summary Report and Risk Assessment Summary/Process Control Strategies shall be reviewed for the need for any updates based on conclusions of packaging process verification activities during Exhibit/Pre-Validation/Pre-PPQ batches, and updated, if required, with justifications. The qualified ranges may be revised, if needed, and the revised ranges/reason for revisions shall be documented clearly in the Packaging Process Design Summary Report which shall be updated thereof.

- **Stage 2 (Process Qualification):**
- The following activities shall be conducted as a part of Stage 2 of Packaging PV, as applicable, based on type of packaging:

Phase	Important Activities
IV	❖ Approval of proofs for production run of printed components ❖ Procurement of components as per approved proofs/specifications ❖ Smooth run of components on production shop floor during PPQ batches

- During Stage 2, the finalized ranges of packaging process parameters and packaging process controls shall be used for verification, and established during the PPQ batches of the product.

- Post PPQ batches, master packaging records shall be revised to include both design space, observed ranges and rejection limits (as applicable) during execution of PPQ batches as target ranges or only to incorporate observed ranges during execution of PPQ batches. If any CPP shows excursion from the validated range but is within Design Space, then impact assessment shall be done.

- Identified CPPs shall be monitored against the design space range during execution of 10 commercial batches (after PPQ batches) and ranges observed during PPQ batches. Ranges shall be revised after the execution of 10 batches or one year (whichever is earlier) for further commercial batches. In case only observed ranges are incorporated in the batch records post PPQ execution, then there is no need to monitor next 10 batches.

- Rejections shall be monitored and recorded along with type of defects for the PPQ batches.

- The packaging process length shall also be specifically considered while drawing samples in order to verify the variability of parameters at different ¥stages of the packaging process, e.g. the start, middle and end of a blistering process.

- The Packaging Process Design Summary Report, Risk Assessment Summary/Process Control Strategies and Packaging Instructions shall be reviewed for the need for any updates based on conclusions of packaging process verification activities during PPQ batches, and updated, if required, with justifications. The qualified ranges may be revised, if needed, and the revised ranges/reason for revisions shall be documented clearly in the Packaging Process Design Summary Report which shall be updated thereof.

- **Stage 3 of PV (CPV)**
- CPV of the Packaging Process shall be carried out as explained for applicable parameters.
- Additionally, rejection trend analysis shall be performed at defined frequencies with respect to the rejection limits / types of rejections study conducted during

- Stage 1 and 2 of the Primary Packaging PV. Appropriate actions based on this trend analysis shall be initiated to reduce packaging defects and ensure continued assurance.

6. Closure and Post Transfer Phase

- Technology transfer can be considered successful if there is documented evidence that the RU can routinely reproduce the transferred product, process or method against a predefined set of specifications as agreed with the SU.

- Technology transfer is considered as successful if the following criteria is met:
    - Product quality that meets the pre—established criteria
    - Process performance is as expected when compared with historical data.
    - Confirmation that the control strategy is executable and it delivered the product meeting CQAs and specifications
    - Successful analytical method validation / verification
    - The additional batch(s) required shall also be part of the Technology Transfer closure assessment. Number of batches based on discussion between RU & SU.
    - After approval of product by regulatory agency, technology shall be considered as transferred to site.

- Post Transfer Phase (Continued Process Verification):
    - The goal of this stage is continual assurance that the process remains in a state of control (the validated state) during commercial manufacture.
    - A system or systems for detecting unplanned departures from the process as designed is essential to accomplish this goal.
    - Adherence to the CGMP requirements, specifically, the collection and evaluation of information and data about the performance of the process, will allow detection of undesired process variability.
    - Evaluating the performance of the process identifies problems and determines whether action must be taken to correct, anticipate, and prevent problems so that the process remains in control.

14 Reference

1. International Council for Harmonisation Q8 (R2) Pharmaceutical Development
2. International Council for Harmonisation Q9 Quality Risk Management
3. International Council for Harmonisation Q10 Pharmaceutical Quality System
4. International Council for Harmonisation Q12 Life Cycle Management
5. International Council for Harmonisation Q14 Analytical Procedure Development
6. Good Practice Guide: Technology Transfer
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8. WHO guidelines on the transfer of technology 6 in pharmaceutical manufacturing
9. USFDA Guidance for Industry Process Validation: General Principle and Practices
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11. Overview of Packaging validation for Drug Products – ISPE
12. Packaging Performance Qualification - A Risk Based Approach, Journal of Validation Technology [Spring 2009]
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14. Understanding Pharmaceutical Quality by Design by Lawrence X. Yu in AAPS J. 2014 Jul; 16(4): 771–783.

Annexure I
Content of knowledge sharing

Annexure II
Exhibit batch initiation checklist

Annexure III
Process Parameter to be considered during Technology Transfer

Annexure IV
Product Launch checklist

Annexure V
Site Transfer checklist

Annexure VI
Process Parameter for Packaging Validation (Blister & Bottle Packaging)

Annexure VII
Technology Transfer Dos and Don’ts

Annexure VIII
Training Needs for Technology Transfer

Appendix I
Content of Knowledge Sharing

Sr. No	Information
	API related and General information
1	Impact of API particle size on product performance
2	Effect of API quality attributes variation on product performance
3	API degradation study - Acid, alkali, temperature, light etc
4	Effect of different API vendors on product performance if multiple vendors are planned
5	API BD, TD and particle size data for 3 batches
6	API COA (in house and Vendor) of at least 3 batches and stability data
7	API solubility study data and impact of PH on solubility
8	API Melting point and Polymorphism data
9	API toxicological data
10	Rationale of selection of different excipient and their role in formulation
11	Innovator's details - Average weight / Shape/Size/Embossing details/excipients/DT and comparison with our product
12	Dissolution data comparison with Innovator vs Test (Bio batch)
13	Innovator stability study data if done
14	Storage condition for granules, blend and tablet
15	Preformulation study data
16	Blend BD, TD and PSD data
17	Blend Angle of Repose
18	Blend Carr's index
19	DOE study data for Process /Formula optimization
20	CPP/CQA / CMA / Overall Risk assessment & Mitigation Plan
21	Hygroscopic study of Drug substance and Drug product
22	LOD theoretical calculation and co relation with water content
23	Stability data of three batches including pilot bio batch
22	Hold time Study data & if stability data of hold time batch if done
23	Residual solvent data of development batches, if any organic solvents are used.
24	Specific Environmental condition during Mfg., like Temp, RH, Sodium light, Oxygen scavengers, silica bags, triple laminated bags or any other condition of bulk storage as well as samples handling for sample to QC
25	Product Development history with respect to issues faced
	Dry Mixing
1	Challenge study for Mixing time vs Blend uniformity
2	BD, LOD & Theoretical Water content of dry mix / blend
	Binder preparation and Addition
1	Challenge study for binder quantity optimization, Binder addition rate & Solvent quantity optimization study
2	Viscosity of binder solution
3	Effect of Hold time of binder at particular duration shall be studied, depends on nature binder, concentration etc.
	Granulation Process (RMG Granulation)
1	Challenges study for deciding factor for optimize high & low kneading, Impeller & chopper speed & its effect on physical & chemical parameters of tablets
2	Impact of granulation challenges on property of finished product and granulometry like bulk density, TD, PSD, Flow property of granules?
3	Granulation end point criteria /characteristic/organoleptic properties/Wet milling requirement if any

Sr. No	Information
	Granulation Process (FBP Granulation)
1	Challenges study to optimize Spray Rate, Atomization pressure, Air Flow, Gun nozzle size & position
	Drying
1	Challenge study to optimize high & Low % LOD & its effect on physical & chemical parameters of tablets
2	Drying sequence and impact on LOD
3	Requirement of Air drying /Racking
4	Requirement of RH during drying (in case of solvent/s used in granulation)
	Dry Granulation (Roll Compaction)
1	Challenge study to optimize Roll pressure, Roll gap, Feed rate
	Sizing/Milling
1	Challenge study to optimise screen size & its effect on physical & chemical properties of the tablets
2	Particle size distribution and BD of Sized granules
3	Any observation of Heat generation during milling
	Blending/ Lubrication
1	Challenges study to optimise blending & Lubrication time, different concentration of lubricants & its effect on physical & chemical parameters of the tablets
2	Risk of lump formation & agglomeration
3	Blend uniformity results at different time interval
4	Physical parameters of blend such as BD, TD, PSD and Angle of repose
	Compression
1	Challenge study of low & high hardness & its impact on physical & chemical parameters of tablets (Dissolution)
2	Correlation between Disintegration time and Dissolution vs Hardness data
3	Effect of Temperature and RH on Tablet parameters
4	Any abnormalities observed during development like flow problem, sticking, picking, Punch jamming etc.
5	Dwell time calculation DT (msec)= (PHFxNPx3600000)/ (π x PCD xTPH) PHF- Punch head flat NP- No of punches π- Press speed in terms of tablets per hour PCD- Pitch circle diameter of the turret TPH- Press speed in terms of tablets per hour
6	Breakability Test data, for low, high, optimum hardness
	Coating
1	Challenges study of low & high coating weight gain, spray rate & % solid content its effect on physical & chemical parameters of tablets
2	LOD of the tablet before and after preheating, after coating and after post coating drying.
3	Viscosity of coating solution
4	Hold time study of coating suspension
5	Tablet specimen sample of final development Batch
6	Residual solvent data in case of solvents to be used

Sr. No	Information
	Drug coating/Seal Coating /Delayed release coating
1	Challenge study for inlet temp, product temp, spray rate, Atomization pressure, Air flow, column height and % wt. gain and its impact on physical & chemical parameters of tablets/capsules
2	Base plate, Bottom sieve, Nozzle diameter and the type of the filter bag used for development batch
3	Bulk density, Tapped Density and PSD of drug coated pellets/Seal coated /delayed release pellets
4	LOD / Water Content data
5	Residual solvent data for R & D batches
6	Any specific requirement for RH during coating and data on lower and higher RH
7	Assay /Dissolution of Under size and over size pellets for functional coating stage.
8	Hold time data for each stage if done in R & D
	Encapsulation
1	Effect of Temperature and RH on Capsule filling
2	Type of capsule filling machine used in R & D
3	List of issues during capsule filling
4	Bulk Density of blend and co relation with capsule size selected
5	Weight variation data of development batches
6	Disintegration test results for development batches
7	Different slug hardness DT and dissolution for capsules
	Analytical Method - Dissolution
1	Dissolution at different RPM of paddle / basket
2	Dissolution profile time point (Release and stability)
3	Effect of temperature of dissolution media
4	Effect of change over (from acid to buffer) - time / rinsing method on dissolution
5	Effect of pH of dissolution media on dissolution
6	Dissolution method Manual vs Autosampler study data
7	For capsule product, dissolution with & without sinker, with and without enzyme
8	Visual observation during dissolution like mass remaining, pellicle formation, capsule rupture time , hazy solution
	Analytical Method /Transfer /Validation
1	BU method for both powder & slug - data
2	Blend Uniformity - Blend Assay - impact of Sample Size
3	FP Assay and FP CU method comparison
4	PSD - Type of Sieve / Sieve Shaker / Time / Quantity of sample
5	Impact of sonication time study on assay /BU
6	Storage condition for standards, impurities and any specific information/precautions for handling
7	Method validation and transfer data
	Packaging Development
1	Type of packing (Strip/blister/ bulk/Bottle)
2	Vibration study if any done in R & D for bottle pack
3	Details of packing material along with specification
4	Transportation study if any done
5	Specific requirement during packaging e.g. nitrogen purging, Thermal seal inspection requirement.
6	Head space for different bottle packs

Appendix II
Checklist for EB Initiation

Sr. No.	Document Name	Reference Document No.	Responsibility	Remarks
1	Product Allocation Form			
2	Toxicological Report for ADE value			
3	Product Manufacturing g Area identification (General/Potent/Hormone)			
4	Cytotoxic / Sex Hormone products- Deactivation agent and deactivation study report.			
5	Manufacturing License (Form 29)			
6	Product Name			
7	Market			
8	Dosage Form			
9	Brand Name			
10	Generic Name			
11	Strength of Product. (if Multiple strength write all)			
12	Pharmacological Category of Product			
13	BFE Code (Strength wise)/SAP code			
14	NDA/ANDA Category (Para I/II/III/IV)			
15	BCS Class			
16	Name of API & % in formulation			
17	Largest daily dose of Product.			
18	Product development data from R & D			
19	Initial Risk assessment from R & D			
20	Batch size in Kg & Units (Scale Up/Exhibit batch/Intended (commercial)			
21	Target weight of tablet /Capsule for each strength			
22	Manufacturing Instructions (Dry Mix/Dry Granulation/Wet Granulation/Top spray/Bottom spray/Spray dryer/HME)			
23	Equipment details -Manufacturing /Packaging			
24	Brief manufacturing process with Flow chart			
25	Manufacturing stage wise -Environmental conditions			
26	Specific precaution/safety measures to be taken during Dispensing/Manufacturing/ Packaging of product.			
27	API/RM/PM Details (Release status)			
28	MSDS (API/RM)			
29	Dry Mix/Blend/Core Tables /Coated Tablets Bulk density data			
30	Tooling details (Drawing) with special requirement (Type of steel/Coating/Tapered dies) if any			
31	Specific requirement (Nitrogen purging/ chilled water/steam Sodium Vapour etc.)			
32	Scale up batch Report review			
33	Cleaning method validation			
34	Packaging change parts (Art work)			
35	Plant presentation			

Analytical				
1	Availability of Column, Reference standard, reagents			
2	Specific instrument availability for analysis of API/RM/PM/DP			
3	Analytical Method Transfer (API/FP)			
4	MLT method Transfer			
Documentation Before EB - for Trial/Scale up batch				
1	Detailed Sheet for API/RM Procurement			
2	MFC/BOM -Trial and Scale up batch			
3	New Product Introduction form			
4	Change control Initiation			
5	Change control for Trial/scale up batch			
6	Trial/Scale up Batch BOM/BMR			
7	Trial/Scale up Batch - Protocol			
8	Trial/ Scale up Report			
Documentation For Exhibit batch				
1	API/RM/PM /IP/FP/Stability /hold time specification and ATP			
2	Specification availability & comparison (in case of multiple market)			
3	New Product Introduction form			
4	Change control Initiation			
5	Master Formula card			
6	Master packaging card			
7	Updated Risk Assessment after scale up			
8	CMA/CPP/CQA			
9	Hold time checklist			
10	Change control for Exhibit Batch BMR			
11	Exhibit Batch BMR/BPR/Protocol			
12	Placebo Bill of Material /Manufacturing/Packaging			
13	Stability study plan (Stability /Photo stability /In use)			
14	Stability Protocol /In-use study protocol			

Appendix III

Process Parameter to be considered during Technology Transfer

Pharmaceutical unit operation

Blending/Mixing			
Input material attributes	Fixed Process parameters	Scalable Process Parameter	Quality attributes
Particle size distribution	Type of Blender	Geometry of blender	Physical Appearance
Bulk/tapped/true density	Order of addition	Mixer load level	Blend uniformity
Electrostatic properties	Agitating bar (on/off pattern)	Number of revolutions (time and speed)	Blend Assay
Moisture content	Discharge method		Particle size
	Holding time		Particle size distribution
	Environment temperature and RH		Bulk/tapped/true density
			Moisture content
			Dissolution

Size Reduction/Comminution			
Input material attributes	Fixed Process parameters	Scalable Process Parameter	Quality attributes
Particle/granule size distribution	Impact/cutting/screening mills		Physical Appearance
Bulk/tapped density	Mill type	Speed	Particle/granule size distribution
Electrostatic properties	Blade configuration, type, orientation	Feeding rate	Bulk/tapped/true density
Moisture content	Screen size and type		API polymorphic form
Granule density (For milling of Roll Compact)	Fluid energy mill		Electrostatic properties
	Number of grinding nozzles	Feed rate of Solid	Related Substances
	Design of Classifier	Nozzle pressure	Blend uniformity
	Position of Nozzle		Blend Assay
			Dissolution

Wet Granulation			
Input material attributes	Fixed Process parameters	Scalable Process Parameter	Quality attributes
Particle size distribution	High/low shear granulation		Physical Appearance
Bulk/tapped density	Type of granulator (High/low shear)	Fill level	Endpoint measurement (e.g., power consumption, torque, etc.)
Moisture content	Spray nozzle type and location	Pregranulation mix time	Blend uniformity
Electrostatic properties	Method of granulating liquid addition (spray or pump)	Granulating liquid or solvent quantity	Assay
	Granulating liquid temperature	Impeller speed, tip speed, configuration, location, power consumption/torque	Moisture/Solvent content (LOD/Residual Solvent)
	Bowl temperature(jacket temperature)	Chopper speed, configuration, location, power consumption	Particle size and distribution
		Granulating liquid addition rate and time	Bulk/tapped density
		Wet massing time (post-granulation mix time)	Related Substances
		Post mixing time	Dissolution
	Fluid bed granulation		
	Type of fluid bed	Fill level	
	Inlet air distribution plate	Granulating liquid quantity	
	Spray nozzle (tip size, type/quantity/ pattern/configuration/position)	Granulating liquid spray rate	
	Filter type and orifice size	Inlet air volume	
	Bottom screen size and type	Atomization air pressure	
	Preheating temperature/time		
	Granulating liquid temperature		
	Granulating liquid concentration/viscosity		
	Granulating liquid holding time		
	Inlet air temperature, dew point		
	Product and filter pressure differentials		
	Product temperature		
	Exhaust air temperature, flow		
	Filter shaking interval and duration		

Drying			
Input material attributes	Fixed Process parameters	Scalable Process Parameter	Quality attributes
Particle size, distribution	Fluidized bed Dryer		Physical Appearance
Electrostatic properties	Inlet air temperature, dew point	Inlet air volume	Granule size and distribution
Moisture content	Product temperature	Drying time	Bulk/tapped density
	Exhaust air temperature,	Load	Moisture content
	Filter type and orifice size		Residual solvents
	Shaking interval and duration		Blend Uniformity & assay
			Related Substances
	Tray		Dissolution
	Type of tray dryer	Bed thickness/tray depth (depth of product per tray)	
	Drying temperature	Trays per chamber/Spacing between Tray	
	Inlet dew point	Quantity of product per tray	
		Drying time	
		Air flow	
	Vacuum/microwave		
	Jacket temperature	Impeller speed	
	Condenser temperature	Bleed air volume	
	Microwave power	Vacuum pressure	
	Electric field	Total drying time	
	Energy supplied		
	Product temperature		
	Bowl and lid temperature		

Roller compaction			
Input material attributes	Fixed Process parameters	Scalable Process Parameter	Quality attributes
Particle size, distribution	Type of roller compactor (fixed roller gap or variable)	Auger (feed screw) speed	Ribbon appearance
Electrostatic properties	Auger (feed screw) type/design (horizontal, vertical or angular)	Roll gap width (e.g., flexible or fixed)	Ribbon thickness
Bulk/tapped density	Deaeration (e.g., vacuum)	Roll pressure (Hydraulic Pressure)	Ribbon density
Moisture content	Roll shape (cylindrical or interlocking).		Particle size Distribution, B.D, T.D
	Roll surface design		Compressibility (Hardness at Compression stage)
	Roll speed		Blend Uniformity & Assay
	Roller temperature		Dissolution
	Fines recycled (yes or no, # of cycles)		
	Pre & Fine granulator speed		
	Pre & Fine granulator sieve		

Extrusion–Spheronization			
Input material attributes	Fixed Process parameters	Scalable Process Parameter	Quality attributes
Particle size, distribution	Type of extruder (screw or basket)	Extruder Screw speed (rpm)	Physical Appearance (Extrudate - Spherical, dumbell, stick etc.)
Electrostatic properties	Screw blade configuration	Extruder Feeding rate (g/min)	Density
Bulk/tapped density	Die or screen configuration (e.g., radial or axial)	Spheronizer load level	Moisture content
Moisture content	Screen opening diameter (mm)	Spheronizer Plate speed	Blend Uniformity & assay
	Screw length, pitch, and diameter	Spheronizer time (Residence time)	Pellets after spheronization
	Number of screws (single/dual)		Pellets size and distribution
	Die length/diameter ratio		Pellets shape factor (e.g. aspect ratio)
	Type of Spheronizer		Bulk/Tapped density
	Plate groove design (spacing and pattern)		Friability
			Dissolution

Hot Melt Extrusion			
Input material attributes	Fixed Process parameters	Scalable Process Parameter	Quality attributes
Particle size, distribution	Screw design (twin/single)	Screw speed	Extrudate density
Melting point	Screw opening diameter (mm)	Feed rate	Length/thickness/diameter
Bulk/tapped density	Feeder type/design	Mean residence time	Polymorphic form and transition
Solid form/polymorph	No. of zones		Content uniformity
Moisture content	Zone temperatures		Throughput
	Chilling rate		Dissolution
			Related substances

Tabletting			
Input material attributes	Fixed Process parameters	Scalable Process Parameter	Quality attributes
Particle/granule size and distribution	Type of press (model, geometry, number of stations)		Tablet appearance (Free from defects)
Bulk/tapped density	Hopper design, height, angle, vibration		Tablet weight
Elasticity	Feeder mechanism (gravity/forced feed, shape of wheels, number of bars)		Weight uniformity
Moisture	Feed frame type		Content uniformity
	Feeder fill depth		Hardness/tablet breaking force/tensile strength
	Tooling design (e.g., dimension, score configuration, quality of the metal)		Thickness/dimensions
	Maximum punch load		Tablet porosity/density/solid fraction
	Press speed/dwell time		Friability
	Precompression force		Moisture content
	Main compression force		Disintegration
	Punch penetration depth		Dissolution
	Ejection force		
	Dwell Time		

Encapsulation			
Input material attributes	Fixed Process parameters	Scalable Process Parameter	Quality attributes
Particle/granule size and distribution	Machine type	Machine fill speed	Capsule appearance
Electrostatic properties	Tamping Force	Auger screw design/speed	Weight uniformity
Bulk/tapped density	No. of tamps		Content uniformity
Moisture	Powder bed height		Moisture content
Gelatin Shell aging	Environmental condition - relative Humidity		Slug tensile strength
Gelatin Weight variation			Disintegration
			Dissolution
			Absence of cross linking

Pan coating			
Input material attributes	Fixed Process parameters	Scalable Process Parameter	Quality attributes
Tablet dimensions	Type of pan coater	Pan load level	Coating efficiency
Tablet defects	Pan (fully perforated or partial perforated)	Pan rotation speed	Core tablet weight before and after preheating
Hardness	Baffle (design, number, location)	Inlet air flow rate	Moisture (gain/loss) during preheating
Density	Spray nozzle (type, quantity, pattern, configuration, spray pattern)	Total spray rate	Coating (polymer and /or color) uniformity
Moisture content	Nozzle to bed distance	Atomization air pressure	% weight gain
Debossing/Embossing on tablets	Distance between nozzles	Pattern air pressure	Film thickness
	Nozzle orientation		Hardness/breaking force/Tensile strength
	Preheating time		Friability
	Inlet air temperature, dew point		Moisture (gain/loss) during overall process
	Product temperature		Residual solvent(s)
	Individual nozzle spray rate		Disintegration
	Exhaust air temperature, air flow		Dissolution
	Curing time and drying time		Tablet defects
			Related Substance

Fluid bed coating			
Input material attributes	Fixed Process parameters	Scalable Process Parameter	Quality attributes
Pellets Particle Size & Distribution	Type of fluid bed coater	Fluid bed load level	Coating efficiency
Pellets Friability	Partition column diameter & height	Inlet air flow rate	Moisture (gain/loss) during preheating
Moisture content	Number of partition columns	Total spray rate	Coated Pellet appearance
Density	Air distribution plate type and size	Atomization air pressure	% weight gain (Correlation with assay)
	Filter type and orifice size	Spray rate per nozzle	Color uniformity
	Filter differential pressure		Friability
	Filter shaking interval and duration		oversize (Retention)/Undersize & Rejection
	Spray nozzle (type, quantity, pattern, configuration)		Moisture (gain/loss) during overall process
	Nozzle port size		Residual solvent(s)
	Preheating time		Disintegration
	Inlet air temperature, dew point		Dissolution
	Product temperature		Tablet defects
	Exhaust air temperature		Visual attributes
	Curing and drying time		Related Substance

Laser drilling			
Input material attributes	Fixed Process parameters	Scalable Process Parameter	Quality attributes
Size/dimensions	Conveyor type	Conveyor speed	Opening diameter (internal and external)
Polymer type membrane thickness	Laser power		Depth
	Number of pulses		Shape of the opening
	Type(s) of lens(es)		Appearance of Tablet
	One or two sided		
	Number of holes		

Appendix IV
New product launch Checklist

LAUNCH CHECKLIST BEFORE FIRST COMMERCIAL BATCH START UP

Sr. No.	Requirement	Responsibility
1	Mfg. license. (Form-29/Form-25/Form-/other	
2	Narcotics & Psychotropic Substances license and authorizations (if required)	
3	Master Formula Card (MFC) - Packaging material details - Device details	
4	Availability of Raw Material specifications (API & Excipients) & test procedures	
5	Packing Material specifications & test procedures	
6	In-process specifications & test procedures	
7	Finished Product specifications & test procedures	
8	Review of Manufacturing process and Product parameters changes from Exhibit (if any)	
9	Review of API/DP spec changes (tightening) from exhibit (if any) and impact evaluation	
10	Review of the Stability data of the exhibit batches	
11	Review of the DR profile, impurity trend (consistency perspective) wrt EB filed Vs current revised spec.	
12	Review of Pre-validation batch report and proposed parameter evaluation.	
13	Cleaning validation evaluation and review of cleaning agent used if any	
14	Hold time Study at different stages data evaluation and protocol issuance - Impact of scale change	
15	Technical Agreement if to be manufactured at contract manufacturer site (if required)	
16	Technical Agreement with contract testing laboratory	
17	Product stability Protocol	
18	Preparation of BMR/BPR	
19	Process Qualification/ Validation Protocol preparation and approval	
20	Quality Risk Assessment and mitigation plan updation and review before validation	
21	Equipment Change parts/tools Availability for manufacturing and packing	
22	Are the vendors of materials included in the MFC are as per filed dossier	
23	Any special storage condition required in the warehouse	
24	Any specific testing / sampling equipment (new columns / instruments / reagents / chemicals / standards / impurities / accessories	
25	Any new stability requirements (new stability chambers as per stability conditions).	
26	Any deviation / OOS/OOT observation during processing / testing of the exhibit batches	
27	Any special packaging requirement for product/market	
28	Approved artwork (labels/leaflets etc.) availability	
29	Verification of equipment occupancy/capacity in line with proposed batch size	
30	Any Specific facility requirement (dedicated facility/Dedicated AHU/ containment with specific OEL levels etc.).	
31	Any specific storage requirement (RH /temperature, use of black polybag, nitrogen blanketing etc.).	
32	Any specific product handling requirement (use of respirator/ nose mask etc.	
33	Any specific cleaning requirement (cleaning/de-activation etc.).	

LAUNCH CHECKLIST BEFORE FIRST COMMERCIAL BATCH START UP		
Sr. No.	Requirement	Responsibility
34	Any specific manufacturing requirement (any new equipment/accessory/utility not available currently at site. etc.).	
35	Any specific processing requirement for product (requirement for flame proof area, sodium vapour light. etc.).	
36	Elemental impurity data evaluation	
37	Temperature cycling study requirement for product	
38	Safety requirement based on data material safety data sheets reviewed	
39	Transportation study evaluation and proposed plan	
40	Any specific requirement for transportation of the product (refrigerated / no refrigerated conditions)	
41	Review of the approved shelf-life (as per dossier/compliance file)	
42	Extractable / Leachability Study report of product container and closure	
43	Surface area of Gasket - Extractable and leachable for process equipment's	
44	Filter Validation data in case of Injectable product	
45	Review and evaluation of Regulatory commitment especially Breakability / divisibility / F-2	
46	In use study for product and its stability till intended use	
47	Feasibility of instruction for user direction	
48	Assessment of changes in specification post exhibit and post regulatory queries	

Appendix V
Checklist for Site transfer products

Sr. No.	Document Title	Document No.	Enclosed Yes / No
1	Product details like product name, label claim, shelf life, market		
2	Master Formula Card		
3	Master Packaging Card		
4	Manufacturing Batch records		
5	Packaging Batch records		
6	Executed batch records of manufacturing and packing preferably three batches		
7	Specifications (Drug substance, Excipients, Packaging materials)		
8	Product Specification (In-process, Release / Regulatory, Stability specifications)		
9	Tool drawings / change part details (as applicable), in case of capsule products, capsule shell shade and composition copy		
10	Finished product trade dress /CPV Trend		
11	Analytical Method Validation Documents		
12	Cleaning Method Validation Documents		
13	Process Validation Protocols and Reports including Packaging validation		
14	Finished Product pack and Artwork Details		
15	Stability Data and trend		
16	Product Development report if available from receiving site / R & D		
17	Risk Assessment Report		
18	Critical Process Parameters and Critical Quality Attributes		
19	Real Hold time data		
20	Product Development history / Annual Product Review (preferably of last two years), product recalls, market complaint or any other negative or positive trends		
21	Current Regulatory status		
22	Finished product sample of minimum three recent batches		
23	Any other supporting document (if any) Product Quality Complaints, OOS/OOT trend, Unplanned Deviation History		

Appendix VI

Process Parameter for Packaging Validation (Blister pack & Bottle packaging)

Sr. No.	Blister Packing Operation
1	Forming Temperature (Low and High forming temperature)
	Low Forming Temperature could lead to insufficient depth of pockets & high temperature leads to deformation of the foil.
2	Sealing Temperature (Low and High Sealing temperature)
	Sealing of the Aluminium foil depends on the Sealing Temperature. Low Sealing Temperature leads to inadequate sealing resulting in failure of leak test. High Sealing Temperature leads to deformation of the film & adverse impact on the product. Drug Product to be evaluated for any impact of sealing temperature on CQAs
3	Speed (Low and High speed)
4	All blister pockets filled
5	Leak test
6	Over-coding / Overprinting
7	Cutting
8	Type of Knurling
9	Print registration control
10	Function of base and lidding foil
	Cartonator
11	Speed (Low and High speed)
12	Carton formation
13	Challenge test of Pharmacode Carton and Leaflet
14	Presence of Blister and Leaflet in Carton
15	Embossing or over coding of batch details on the carton
	Check weigher
16	Speed (Low and High speed)
17	Under weight and over weight of carton
18	
	Bottle Packing Operation
19	Conveyer/Machine Speed (Low and High speed)
20	Correct No. of Packing component in Bottles (e.g. silica gel or desiccant, cotton)
21	Torque Value
22	% Induction Sealing Power
23	Leak Test
	Check weigher
24	Speed (Low and High speed)
25	Under weight and over weight of carton
	Labelling
26	Pharmacode Challenge test of Bottle label (As Applicable)
27	Barcode Challenge test of Bottle label (As Applicable)
28	Pharmacode Challenge test of leaflet (As Applicable)
29	Barcode Challenge test of leaflet (As Applicable)
30	Bottle without leaflet
31	Overcoding of label
32	Challenge test of Bottle Without label

Appendix VII
TECHNOLOGY TRANSFER DOS AND DON'TS

TECHNOLOGY TRANSFER DOS AND DON'TS

< DOs >

- Cross functional team shall be formed to do the Technology Transfer including representatives from MS&T, Manufacturing, QA, QC & Packaging teams.
- Technology Transfer shall be monitored till successful launch of the product.
- Risk Assessment to be updated at every stage – after scale up , exhibit , pre-engineering /characterization batch and after PPQ batches.
- Risk mitigation before execution of batches
- Review of Development data and Scale up data before exhibit batch execution
- Review of analytical method and validation transfer data before execution of exhibit batches

TECHNOLOGY TRANSFER

< DONTs >

- Do not transfer knowledge only with transferring documents .
- Technology Transfer should not be a one way process.
- Do not Drive process by individual based decision but go by team effort
- Do not Change critical equipment's and batch size at last moment
- Do not Compromise on environmental condition if API or excipients are hygroscopic
- Do not take decision only based on prior experience .encourage team to take decision based on data and statistical evaluation.

2

TECHNOLOGY TRANSFER DOS AND DONTS

< DOs >

- Review of BMR of exhibit , PPQ batches and stability data to finalize commercial batch document.
- Presentation before exhibit batch and PPQ batches to cross functional teams
- Physical observation to be captured for dissolution data /profile generation
- Physical observation during compression , granulation, coating etc – Flow properties, sticking , capping , film cracking , appearance etc
- A comprehensive gap analysis shall be done between sending unit & receiving unit for Technology Transfer.

TECHNOLOGY TRANSFER

< DONTs >

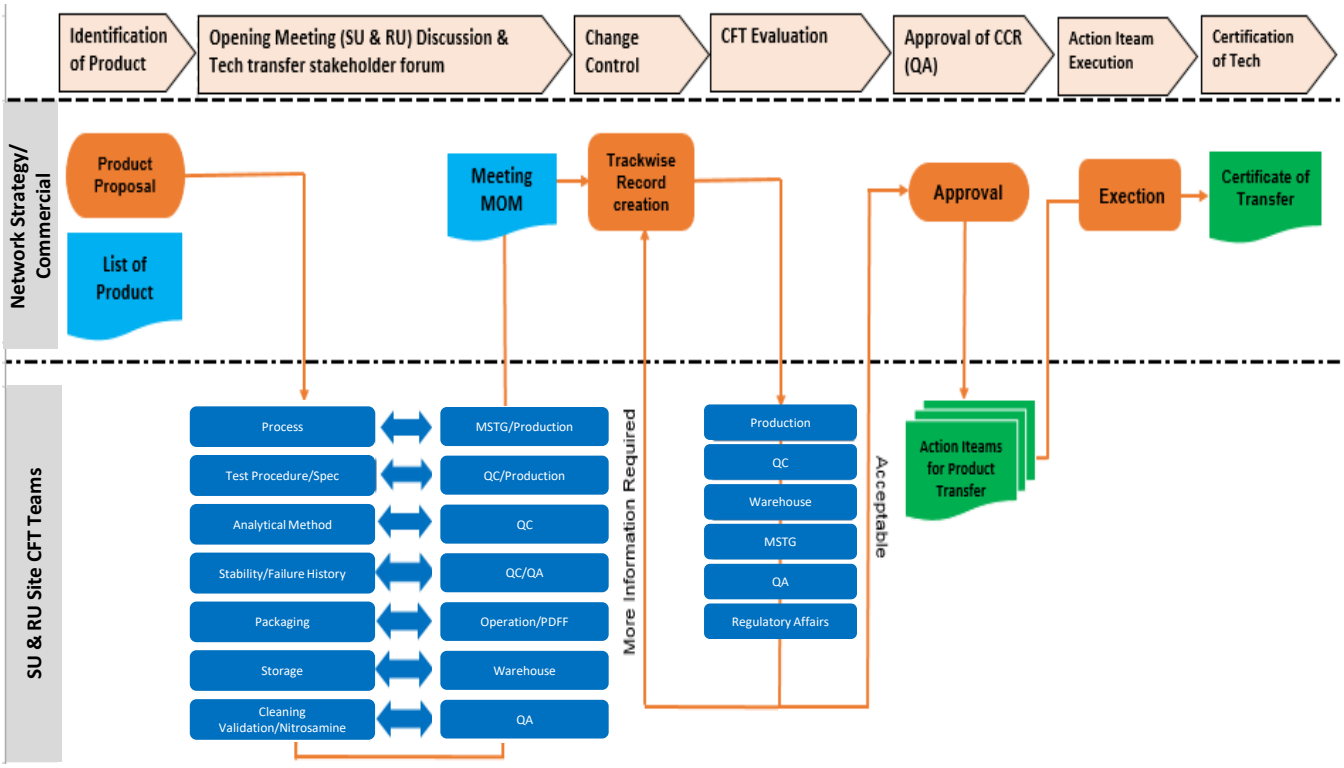
- Do not start exhibit batch before scale up batch data , report , QBD data and development data .

3

Appendix VIII
Training Needs for Technology Transfer

Tech Transfer to Operation, QC and QA	❖ Technical Training product wise before initialing Scale up / Trial batches at plant at the time of Tech Transfer. ❖ Training before Process Validation activity ❖ Training after PPQ report closure & handover to Operation.
Regulatory requirements	❖ Regulatory filing requirements – QA, QC, MSTG ❖ Scale up & post approval changes – QA, QC & MSTG
Critical equipment training	❖ Onsite training for important equipment's, ❖ Scale up factor – Operation and MSTG
Documentation	❖ Training related to documents preparation & review ❖ Good documentation practices
General Training	❖ CGMP training (Plant SOP) ❖ Quality by Design (R & D data) ❖ Statistical evaluation of exhibit batch data ❖ Technical writing Skills ❖ ICH /WHO Guidelines

Product Technology Transfer Process Flow and Milestones (for Site to Site Transfer)



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