TECHNOLOGY TRANSFER DOSAGE FORMS GUIDELINE

IPA
INNOVATION. QUALITY. GLOBAL REACH.

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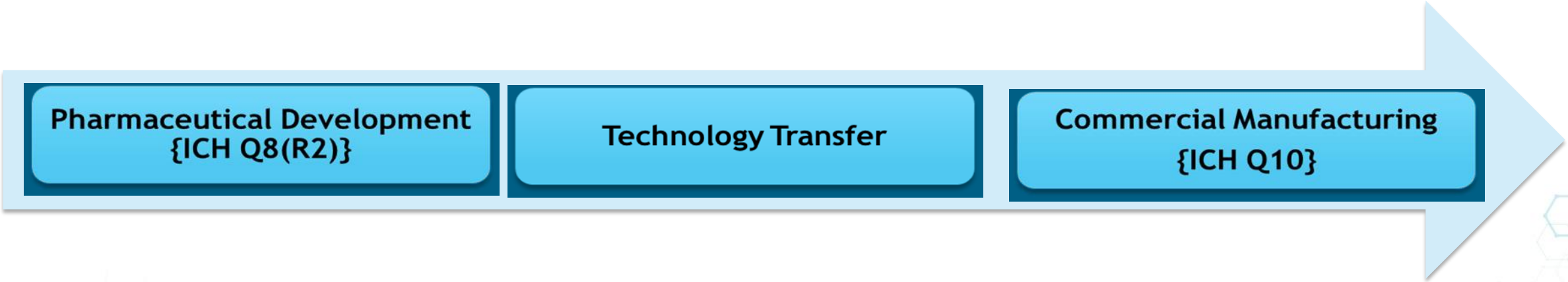
What is Technology Transfer?

- Technology transfer is the process of sharing skills, knowledge, technologies, manufacturing process, analytical methods within or between the organizations.
- In the pharmaceutical industry, “technology transfer” refers to the processes that are needed for successful progress from drug discovery to product development to clinical trials to full-scale commercialization.



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.”

Scope of Technology Transfer:

Technology Transfer

From R&D to Production (Development to Exhibit & PPQ batches manufacturing)

- From R&D scale to Exhibit scale for 1st time.
- No previous experience of Product behaviour at large scale
- Regulatory filing
- E.g. Scale up/Exhibit Batches/PPQ batches

From Small Scale to Higher Scale (Commercial Stage)

- More experience with Product
- Large amount of Data available
- Within Facility from one area to another e.g. 100 L to 600 L
- For Increase in batch size, cost improvement
- PPQ/Commercial batches

From One site to other site (Site Transfer)

- More experience with Product
- Large amount of Data available
- Different Facility, Set of Equipment
- For Regulatory filing, PPQ/Commercial batches

Responsibility Matrix for Technology Transfer:

Contents of Technology Transfer:

The guidelines address the following areas for successful technology transfer at the manufacturing site:

- 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 Knowledge transfer
- Assessment of premises and equipment/instruments
- Documentation
- Qualification and validation

Quality By Design (Qbd): Product & Method Development

- The foundation of robust product starts with Pharmaceutical product development as per ICH Q8(R2) and analytical method development as per ICH Q14. Better understanding of product & analytical method at development stage may assist in successful technology transfer.
- Following are the steps involved in Product and Method Development:

Product Development

Method Development

Phases of Technology Transfer:

Evaluation and Decision

- Finalization of Batch Size & Equipment
- Decision for Technology Transfer
- Planned Approach involving CFT
- Legal and Economic Implication

Planning

- Technology Transfer Team formation
- Availability of Accessories, Raw Material & WS
- Manufacturing Planning
- Knowledge sharing between teams

Preparation

- Data Sharing from R&D (SU) to RU for raw material & Process
- Equipment equivalency & Scale up consideration
- MFC, MPC, Risk Assessment (including CPP & CQA), Stability Protocol,
- Analytical Method Transfer/Validation report

Execution

- Trial (Demonstration batches)/Scale up Batches Execution
- Evaluating feasibility of manufacturing process & equipment
- Exhibit & Process Validation Batches
- Stability Trend monitoring

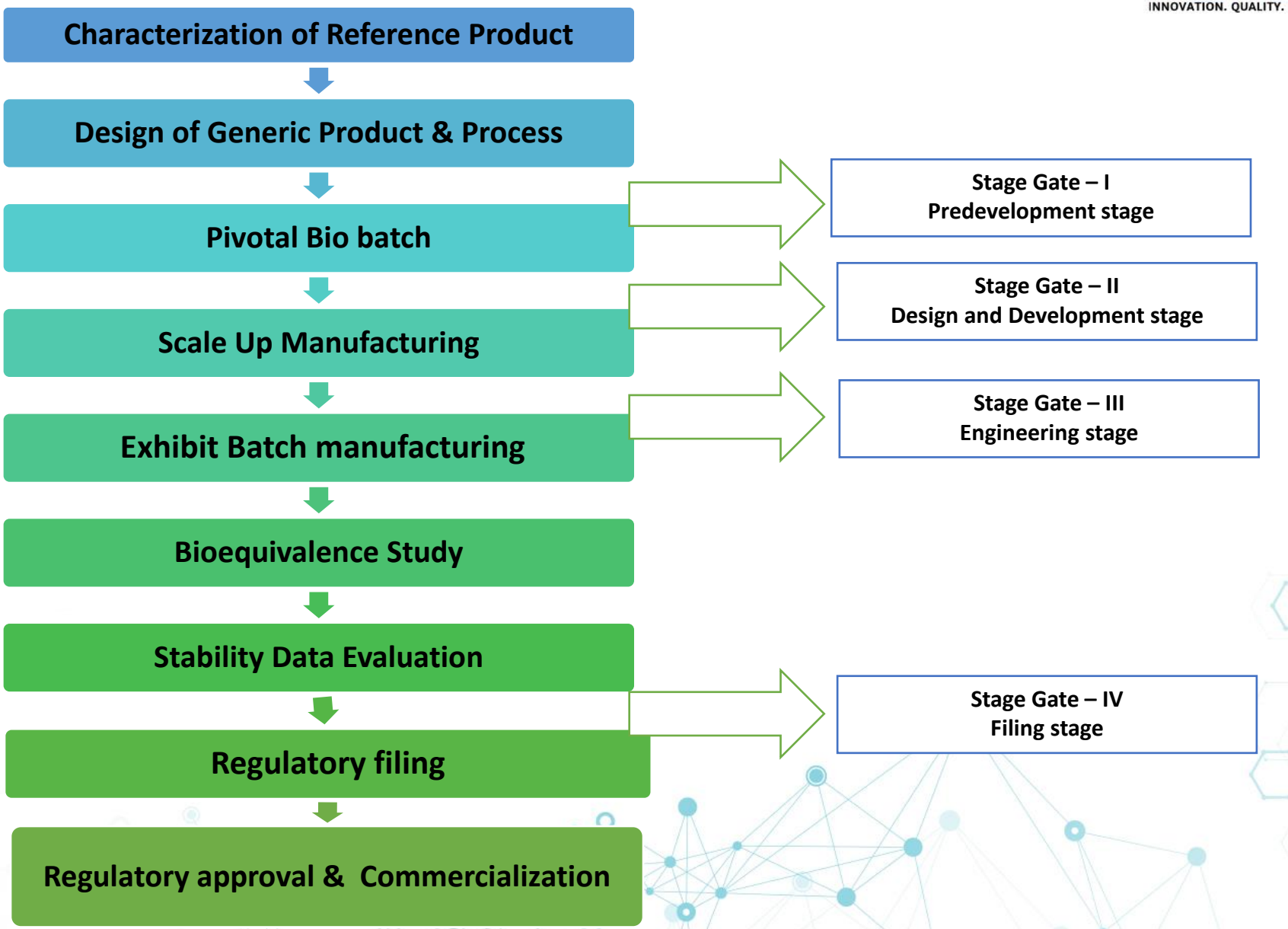
Assessment

- Exhibit/PV batch summary report
- Recommendation for PV/ Commercial Batches
- Regulatory Filing, Response to queries
- Real/sequential Hold time study (if required)

Closure & Post Transfer

- Closure on successful complying pre determine criteria for manufacturing and analytical
- Continued Process Verification

Stage Gate review: A Risk Assessment Process



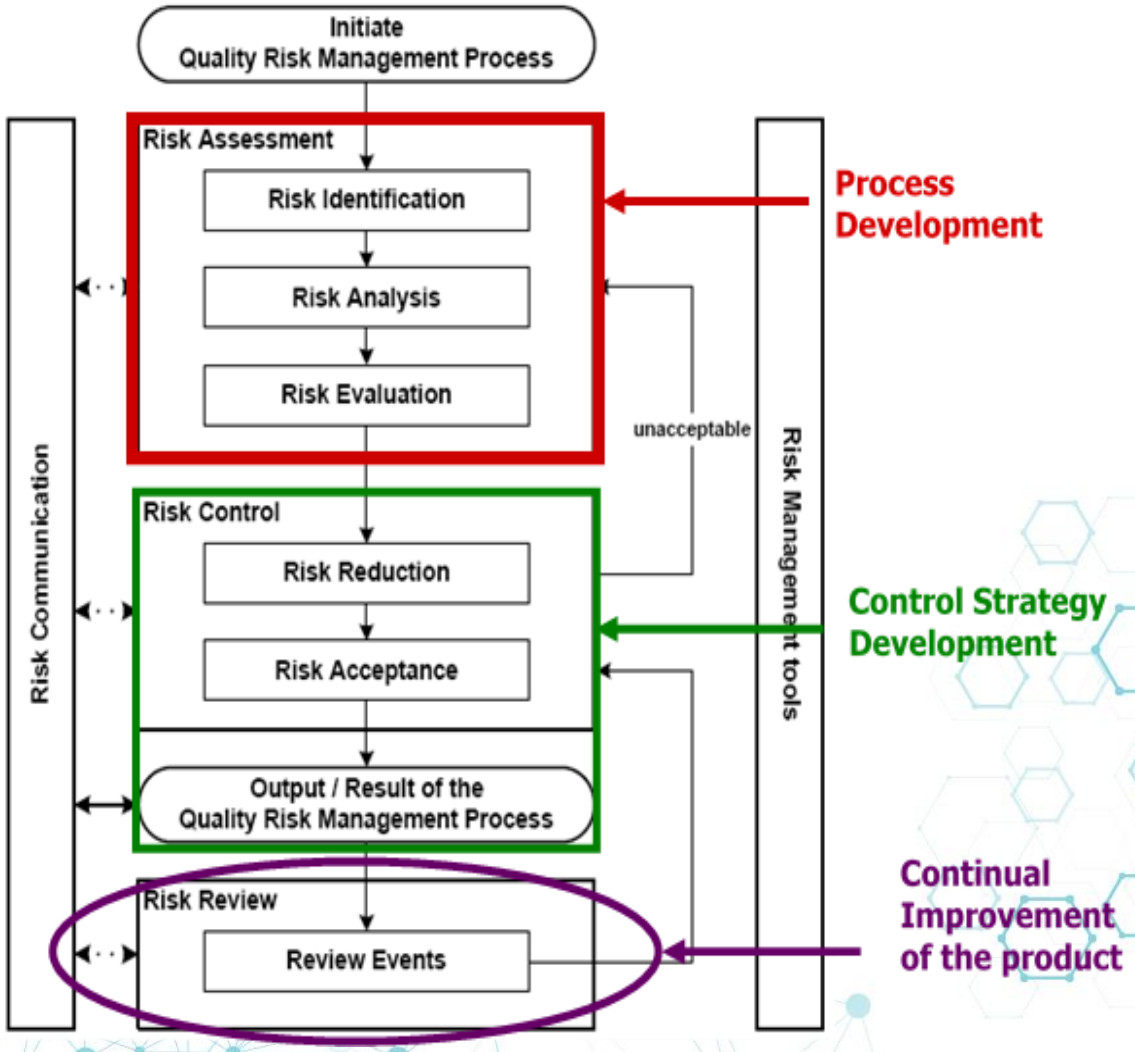
Technology Transfer: Risk Assessment (ICH Q9)

The most important aspects of technology Transfer from one site to another is identifying Gap & mitigation strategy between Sending Unit and Receiving Unit:

Steps in Technology Transfer

1) Identifying Gap (Risk)
2) Risk Analysis & Evaluation
3) Risk Mitigation Plan & Execution

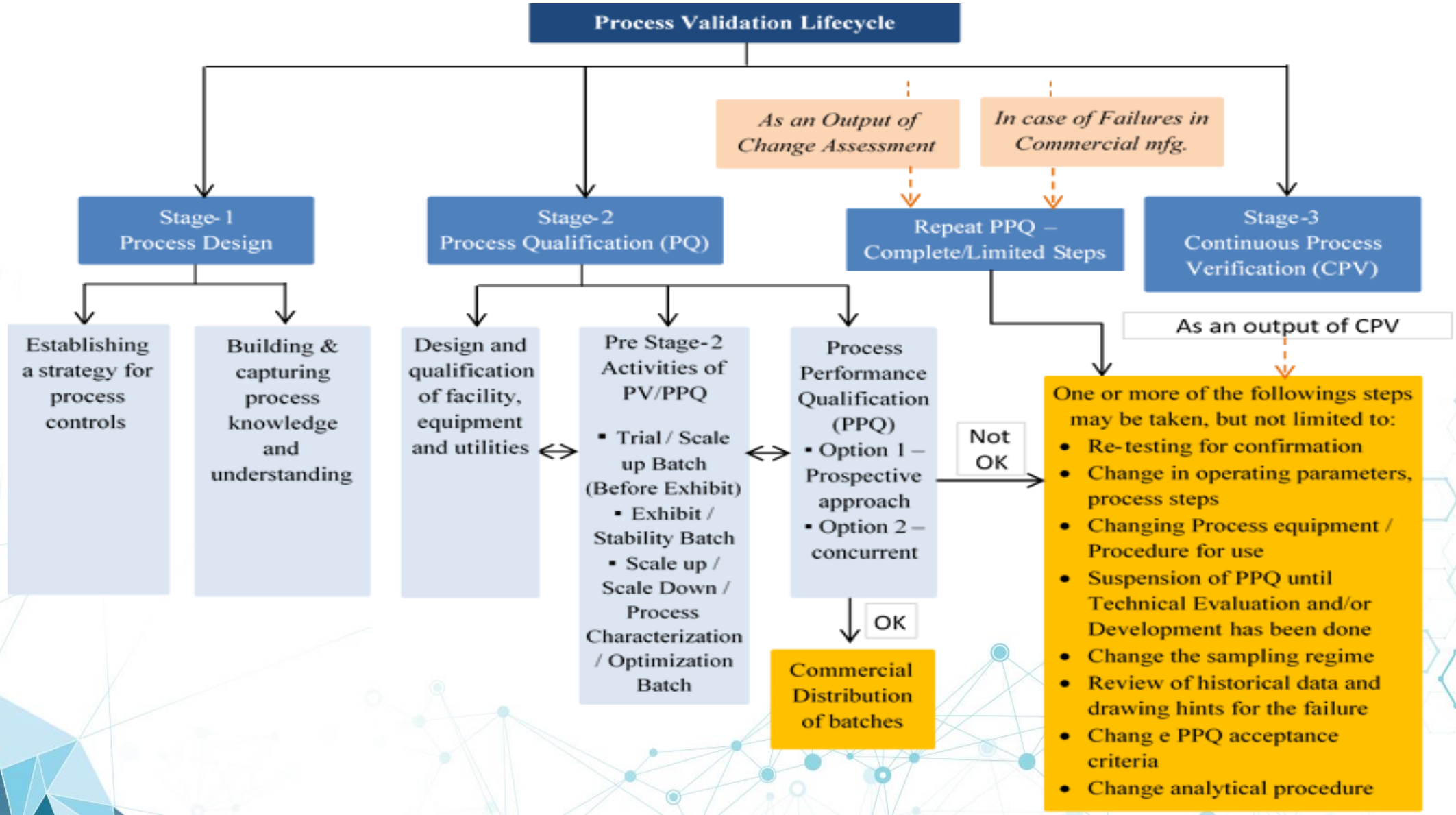
Don't forget to consider scale dependent & equipment dependent parameter.



ICH Q10-Stages of Product Lifecycle Management

- **Stage I: Process Design**
- **Stage II: Process Qualification**
- **Stage III: Continuous Verification**

Flow Chart of Process Performance Qualification (PPQ)/ Process Validation for Drug Product



Process Validation for Packaging

The process of Packaging Validation involves same steps as that of Drug Product:

Stage 1: Process Design

- Feasibility Studies, Development / design studies of new packs
- 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
- Conducting transit worthiness trials / Freeze Thaw study (Wherever required)

Stage 2: Process Qualification

- Qualification of Process Parameter during packaging of Pre-Validation/Pre-PPQ Batches/PPQ Batches
- Rejections shall be monitored and recorded along with type of defects for the Exhibit Batches / Pre-Validation / Pre-PPQ.
- 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

Stage 3: Continuous Process Verification (CPV)

- Identified CPPs shall be monitored against the design space range
- 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.

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 filling requirements – QA , QC , MS&T ❖ Scale up & post approval changes – QA , QC & MS&T
Critical equipment training	❖ On site training for important equipment's, Scale up factor – Operation and MS&T
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

TECHNOLOGY TRANSFER DO & DON'T:

< 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 by 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.

TECHNOLOGY TRANSFER DO & DON'T:

< 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
- Query to be responded based on exhibit batches, QBD , process optimization & scale up batch data and if required additional batch to be made .
- A comprehensive gap analysis shall be done between sending unit & receiving unit for Technology Transfer.
- Facilitate periodic interaction between R & D and plant/between 2 different manufacturing sites.

TECHNOLOGY TRANSFER

< DONTs >

- Do not start exhibit batch before satisfactory evaluation of QBD, Development data , process optimization data & scale up batch data .
- Do not provide team with less time for preparation and evaluation of risk and knowledge transfer.

Technology transfer guideline key Emphasis

Knowledge transfer

- Generation and transfer of knowledge from R&D to MS&T and from MS&T to Operation & Quality team is an essential link for successful technology Transfer.
- Involvement of formulation and Analytical methods at early stages of development can enrich product life cycle.
- Good knowledge of Regulatory guidance & expected queries can make technology transfer process more easier & faster.
- Tech Transfer should be combination of science and experienced based approach

Technology transfer

- Plant and R & D equipment's should have same principle and scalable design to mitigatee the impact of scale change
- Scale up factor to be applied to all critical equipment's.
- Lab Scale data from QbD (Product + Analytical) to considered for finalizing process parameters & methods
- Risk assessment and gap identification if key factor to prevent failure.
- Mitigation and Control Strategy shall be in place for successful completion of Exhibit /PPQ Batches.
- Technology Transfer should be more data driven with the use of Statistical tools.

Checklist

- Evaluation of requirement like facility/ Equipment/ Man/ Material to be assessed before initiation.
- Method transfer by ADD in person and effective knowledge transfer to NPQC.
- Complex products ADD scientist required for Scale up & or exhibit batch analysis.
- All technical changes during life cycle management to be driven through MS&T.
- Skill enhancement and Training is must for person involved in technology transfer.
- Stage wise, process wise checklist shall be followed while product & process evaluation.

Conclusion:

"It is a collaborative effort with Research and Development, Manufacturing Science & Technology, Quality, Manufacturing, Engineering etc. that is needed to assure a successful technology transfer and a Robust final manufactured product"

- George P. Milli- Merck

Technology transfer can be considered successful if a receiving unit (plant, lab) can routinely reproduce the transferred product, process, method against a predetermined set of specifications as agreed with the sending unit or a development laboratory

- ISPE Good Practice Guide : Technology Transfer

REFERENCES

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
7) WHO guidelines on the transfer of technology in pharmaceutical manufacturing
8) WHO guidelines on the transfer of technology 6 in pharmaceutical manufacturing
9) USFDA Guidance for Industry Process Validation: General Principle and Practices
10) European Medicine Agency: Guideline on Process validation for finished product
11) Overview of Packaging validation for Drug Products – ISPE
12) Packaging Performance Qualification - A Risk Based Approach, Journal of Validation Technology [Spring 2009]
13) TECHNOLOGY TRANSFER IN PRACTICE by Stewart Green and Paul Warren Quality Division of Wyeth Pharmaceuticals Havant, UK
14) Understanding Pharmaceutical Quality by Design by Lawrence X. Yu in AAPS J. 2014 Jul; 16(4): 771–783.

THANK YOU