STUDY MATERIAL
BP 702 T. INDUSTRIAL PHARMACYII (Theory)
Unit - II

Syllabus

Technology development and transfer: WHO guidelines for Technology Transfer(TT): Terminology, Technology transfer protocol, Quality risk management, Transfer from R & D to production (Process, packaging and cleaning), Granularity of TT Process (API, excipients, finished products, packaging materials) Documentation, Premises and equipments, qualification and validation, quality control, analytical method transfer, Approved regulatory bodies and agencies, Commercialization - practical aspects and problems (case studies), TT agencies in India - APCTD, NRDC, TIFAC, BCIL, TBSE / SIDBI; TT related documentation - confidentiality agreement, licensing, MoUs, legal issues.

Technology Development and Transfer

Abstract

In today's scenario, interest in the profitable exploitation of a firm's technological assets, through technology transfer, has intensified. Appropriate technology transfer is both vital and critical to drug discovery and development for novel medicinal products and is also essential to upgrade drug quality intended during research and development and to finishing product during manufacturing as well as to assure constant quality transferred. Successful growth and commercialization of innovative technologies is always apprehensive with difficulties, multifaceted endeavor, and a range of development tools exist to uphold this activity, by far the most popular approach to directly supporting successful innovation is through technology transfer. To develop appropriate clinical good manufacturing practice facilities, specify and design specialized process equipment, finalize process details, and correctly determine scale-up parameters requires the integrated efforts of a highly skillful technology transfer team. Successful technology transfer requires carefully studying conditions like careful evaluation of ultimate manufacturing requirements early in research and development and the consequent improvement of robust developments that endure large-scale operation, the assembly of a detailed technology transfer document that provides manufacturing with both "know how" and "know why," and will serve as the basis for facilities and equipment design as well as operator training and standard operating procedure generation in successful manufacturing.

Introduction

What is technology transfer?

- Transfer of technology is defined as a "logical procedure that controls the transfer of any process together with its documentation and professional expertise between developments or between manufacture sites."
- Technology transfer is both integral and critical to the drug discovery and development process for new medical products.
- Technology transfer is helpful to develop dosage forms in various ways as it provides efficiency in process, maintains quality of product, helps to achieve standardized process which facilitates cost effective production. It is the process by which by an original innovator of technology makes it technology available to commercial partner that will exploit the technology.
- In pharmaceutical industry, "Technology transfer "refers to the processes of successful progress from drug discovery to product development, clinical trials and ultimately full scale commercialization.
- Technology transfer is important for such researcher to materialize on a larger scale for commercialization especially in the case of developing product. Technology transfer includes not only patentable aspects of production but also includes the business processes such as knowledge and skills.
- The different stages involved in technology transfer are presented in figure 1.

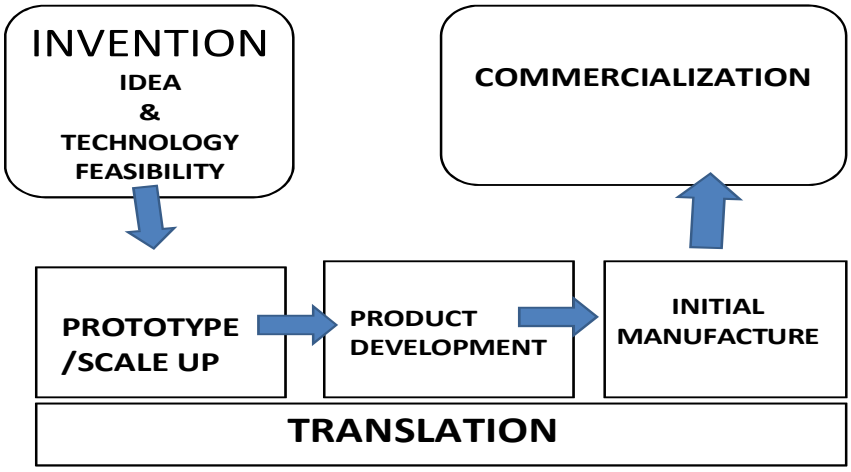

Figure 1, Different stages of technology transfer

Facts of technology transfer

The transfer of technology could happen in following ways

- Government labs to private sector firms.
- Between private sector firms of same country.
- Between private sector firms of different country.
- From academia to private sector firms.

WHO guidelines for Technology Transfer (TT): [1]

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. Focus has been placed on the quality aspects, in line with WHO's mandate.

1. 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.
2. 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". 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.
3. Literature searches revealed little information on the subject originating from national or regional regulatory bodies. Guidance on intra-company transfers was prepared by the International Society for Pharmaceutical Engineering (ISPE).
4. 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 or consolidations and mergers. The WHO Expert Committee on Specifications for Pharmaceutical Preparations, therefore, recommended in its 42nd report that WHO address this issue through preparation of WHO guidelines on this matter.
5. 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 (RU) and the unit managing the process, which may or may not be a separate entity.

6. For successful transfer, 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 (QRM).

   • The capabilities of the SU and the RU should be similar, but not necessarily identical, and facilities and equipment should operate according to similar operating principles.

   • A 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.

7. 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.
8. 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.
9. 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. Any lack of transparency may lead to ineffective transfer of technology.
10. Some of the responsibilities outlined in this document for the SU may also be considered to be part of the management unit responsibilities. The guidelines address the following areas
    - 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.
    - Documentation; and qualification and validation.

Terminologies used in technology Transfer

Acceptance criteria Measurable terms under which test results will be considered acceptable.

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 (C/C) 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.

Corrective action (C/A) 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 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 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 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 drug regulatory authority, intended for the incorporation into the application for marketing authorization.

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 products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

Inter-company transfer A transfer of technology between sites of different companies.

Intra-company transfer A transfer of technology between sites of the same group of companies.

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.

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.

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.

Quality assurance (QA) Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. 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.

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.

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 across 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 where a designated product, process or method is expected to be transferred from.

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).

Transfer of technology (TOT) A logical procedure that controls the transfer of an established process together with its documentation and professional expertise to site capable of reproducing the process and its support functions to a predetermined level of performance.

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 manufacturer's 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.

Technology Transfer Protocol

The transfer protocol should list the intended sequential stages of the transfer. The protocol should include:

- objective;
- scope;

- key personnel and their responsibilities;
- a parallel comparison of materials, methods and equipment;
- the transfer stages with documented evidence that each critical stage has been satisfactorily accomplished before the next commences;
- identification of critical control points;
- experimental design and acceptance criteria for analytical methods;
- information on trial production batches, qualification batches and process validation;
- change control for any process deviations encountered;
- assessment of end-product;
- arrangements for keeping retention samples of active ingredients, intermediates and finished products, and information on reference substances where applicable; and
- Conclusion, including signed-off approval by project manager.

Quality risk management [2]

Two primary principles of quality risk management are:

- ✓ The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and
- ✓ The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle. A model for quality risk management is outlined in the Figure 2.

Responsibilities

Quality risk management activities are usually, but not always, undertaken by interdisciplinary teams. When teams are formed, they should include experts from the appropriate areas (e.g., quality unit, business development, engineering, regulatory affairs, production operations, sales and marketing, legal, statistics and clinical) in addition to individuals who are knowledgeable about the quality risk management process.

Initiating a Quality Risk Management Process

Quality risk management should include systematic processes designed to coordinate, facilitate and improve science-based decision making with respect to risk. Possible steps used to initiate and plan a quality risk management process might include the following :

- Define the problem and/or risk question, including pertinent assumptions identifying the potential for risk;
- Assemble background information and/ or data on the potential hazard, harm or human health impact relevant to the risk assessment;
- Identify a leader and necessary resources;
- Specify a timeline, deliverables and appropriate level of decision making for the risk management process.

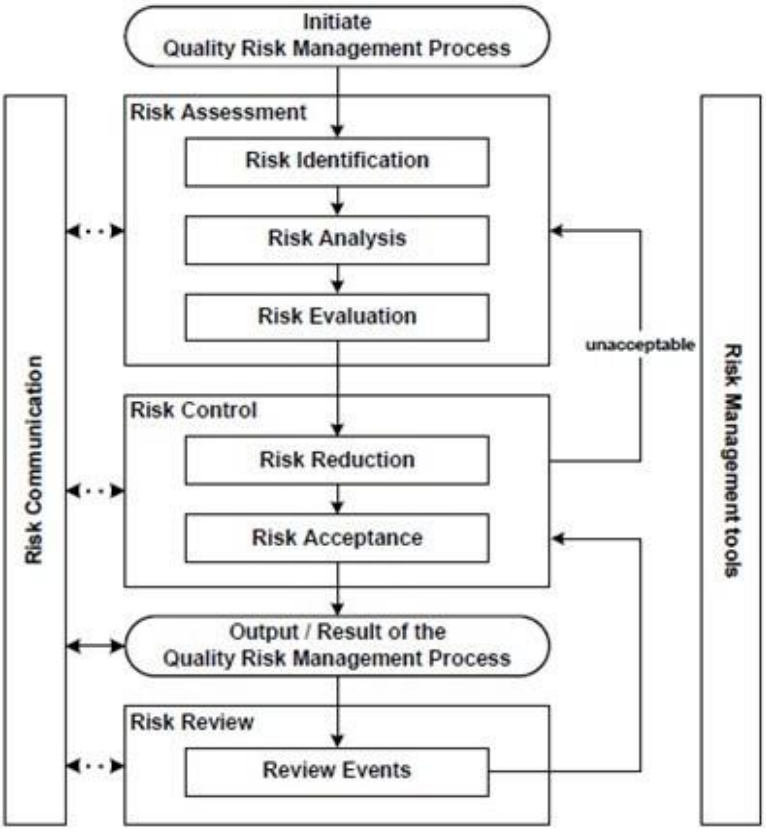

Figure 2, Overview of a typical Quality risk management process

Risk Assessment

Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. Quality risk assessments begin with a well-defined problem description or risk question. Three fundamental questions are often helpful:

- What might go wrong?

- What is the likelihood (probability) it will go wrong?
- What are the consequences (severity)?
- ***Risk Identification***

  It is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders. Risk identification addresses the "What might go wrong?" question, including identifying the possible consequences

Risk analysis

Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms.

Risk Evaluation

It compares the identified and analyzed risk against given risk criteria. The output of a risk assessment is either a quantitative estimate of risk or a qualitative description of a range of risk. When risk is expressed quantitatively, a numerical probability is used. Alternatively, risk can be expressed using qualitative descriptors, such as "high", "medium", or "low", which should be defined in as much detail as possible.

Risk Control Risk control includes decision making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. Risk control might focus on the following questions:

- Is the risk above an acceptable level?
- What can be done to reduce or eliminate risks?
- What is the appropriate balance among benefits, risks and resources?
- Are new risks introduced as a result of the identified risks being controlled?

Risk Reduction

Risk reduction focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level. Risk reduction might include actions taken to mitigate the severity and probability of harm. Processes that improve the detectability of hazards and quality risks might also be used as part of a risk control strategy.

Risk communication

Risk communication is the sharing of information about risk and risk management between the decision makers and others. Parties can communicate at any stage of the risk management

process. The output/result of the quality risk management process should be appropriately communicated and documented.

Risk review

A mechanism to review or monitor events should be implemented. The output/results of the risk management process should be reviewed to take into account new knowledge and experience. The frequency of any review should be based upon the level of risk. Risk review might include reconsideration of risk acceptance decisions.

Risk management methodology

Quality risk management supports a scientific and practical approach to decision-making. It provides documented, transparent and reproducible methods to accomplish steps of the quality risk management process based on current knowledge about assessing the probability, severity and sometimes detectability of the risk. The pharmaceutical industry and regulators can access and manage risk using recognized risk management tools and/or internal procedures (e.g., standard operating procedures). Below is a non-exhaustive list of some of these tools.

- Basic risk management facilitation methods (flowcharts, check sheets etc.);
- Failure Mode Effects Analysis (FMEA);
- Failure Mode, Effects and Criticality Analysis (FMECA);
- Fault Tree Analysis (FTA);
- Hazard Analysis and Critical Control Points (HACCP);
- Hazard Operability Analysis (HAZOP);
- Preliminary Hazard Analysis (PHA);
- Risk ranking and filtering;
- Supporting statistical tools.

Transfer from R & D to production (Process, packaging and cleaning)

- It should be established at the outset whether the intention is to perform single-batch manufacture, continuous production or campaigns, and whether the RU can accommodate the intended production capacity.
- Consideration should be given to the level and depth of detail to be transferred to support production and any further development or process optimization at the RU as intended under the transfer project plan.

- The SU and the RU should jointly develop a protocol for the transfer of relevant information related to the manufacturing process under consideration from the SU to the RU, as well as the development of an equivalent process at the RU.

Process

The SU should provide a detailed characterization of the product, including its qualitative and quantitative composition, physical description, method of manufacture, in-process controls and specifications, packaging components and configurations, and any special safety and handling considerations. The SU should provide any information on the history of process development which may be required to enable the RU to perform any further development and/or process optimization intended after successful transfer. Such information may include the following:

- ***information on clinical development***, e.g. information on the rationale for the synthesis, route and form selection, technology selection, equipment, clinical tests, and product composition;
- ***information on scale-up activities***: process optimization, statistical optimization of critical process parameters, pilot report and/or information on pilot-scale development activities indicating the number and disposition of batches manufactured; and
- ***information or report on full-scale development activities***, indicating the number and disposition of batches manufactured, and deviation and change control reports which led to the current manufacturing.

The SU should provide to the RU information on any health, safety and environmental issues associated with the manufacturing processes to be transferred, and resulting implications, e.g. need for gowning or protective clothing.

The SU should provide to the RU information on current processing and testing, including but not limited to:

- a detailed description of facility requirements and equipment ;
- process technology selection;
- information on starting materials, applicable MSDs and storage requirements for raw materials and finished products;
- description of manufacturing steps (narrative and process maps or flow charts), including qualification of in-processing hold times and conditions, order and method of raw material addition and bulk transfers between processing steps;
- description of analytical methods;

- in-process controls, including, 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;
- validation information, e.g. validation plans and reports, and annual product reviews;
- stability information; and an authorized set of SOPs and work instructions for manufacturing.

Packaging

It should follow the same procedural patterns as those of the production transfer.

- ***Information on packaging*** to be transferred from the SU to the RU include specifications for a suitable container/closure system, as well as any relevant additional information on design, packing, processing or labeling requirements needed for qualification of packaging components at the RU.
- ***For quality control testing*** of packaging components, specifications should be provided for drawings, artwork, and material (glass, card, fibre board, etc.).

Based on the information provided, the RU should perform a suitability study for initial qualification of the packaging components. Packaging is considered suitable if it provides adequate protection (preventing degradation of the drug due to environmental influences), safety (absence of undesirable substances released into the product), compatibility (absence of interaction possibly affecting drug quality) and performance (functionality in terms of drug delivery).

Cleaning

During the manufacturing process, pharmaceutical products and APIs can be contaminated by other pharmaceutical products or APIs if processing different products. To minimize the risk of contamination and cross-contamination, operator exposure and environmental effects, adequate cleaning procedures are essential.

The SU should provide information on cleaning procedures in use at the SU to minimize cross-contamination due to residues from previous manufacturing steps, operator exposure and environmental impact, including: solubility information of active ingredients, excipients and vehicles.

Granularity of TT Process (API, excipients, finished products, packaging materials)

Starting materials

The specifications of the starting materials (APIs and excipients) to be used at the RU should be consistent with reference batches (development batches, biobatches or batches manufactured at the SU). Any properties which are likely to influence the process or product should be identified and characterized.

Active Pharmaceutical Ingredients (API)

The SU should provide the drug master file (DMF) and any relevant additional information on the API to the RU to be checked against the specifications of the API. The following information should be provided:

- manufacturer;
- flow chart of synthetic pathway, outlining the process, including entry points for raw materials, critical steps, process controls and intermediates;
- definitive form of the API (including photomicrographs and other relevant data) and any polymorphic and solvate forms;
- solubility profile;
- partition coefficient (including the method of determination);
- intrinsic dissolution rate (including the method of determination);
- particle size and distribution (including the method of determination);
- bulk physical properties, including data on bulk and tap density, surface area and porosity as appropriate;
- water content and determination of hygroscopicity, including water activity data and special handling requirements;
- microbiological considerations (including sterility, bacterial endotoxins and bioburden levels where the API supports microbiological growth) in accordance with regional pharmacopoeial requirements;
- specifications and justification for release and end-of-life limits;
- summary of stability studies conducted in conformity with current guidelines, including conclusions and recommendations on retest date;
- listing of potential and observed synthetic impurities, with data to support proposed specifications and typically observed levels;
- information on degradants, with a listing of potential and observed degradation products and data to support proposed specifications and typically observed levels;

- potency factor, indicating observed purity and justification for any recommended adjustment to the input quantity of API for product manufacturing, providing example calculations; and
- special considerations with implications for storage and/or handling, e.g. safety and environmental factors and sensitivity to heat, light or moisture.

Excipients

The excipients to be used have a potential impact on the final product. Their specifications as well as the DMF should, therefore, be made available by the SU for transfer to the RU site. The following information should be provided for all types of excipients:

- description of functionality, with justification for inclusion of any antioxidant, preservative or any excipient above recommended guidelines;
- manufacturer;
- specifications, i.e. monographs and additional information that may affect product processing or quality for compendia excipients, or a complete listing of specifications, including analytical methods and justification for release limits for non-compendial excipients. For excipients used for the first time in a human drug product or by a new route of administration, the same level of detail as for a drug substance should be provided;
- special considerations with implications for storage and/or handling, including but not limited to safety and environmental factors (e.g. as specified in material safety data sheets) and sensitivity to heat, light or moisture solubility; and
- regulatory considerations, i.e. compendial status and appropriate regulatory information for non-compendial excipients; information on residual solvents or organic volatile impurities; and documentation to support compliance with transmissible animal spongiform encephalopathy certification requirements (where applicable).

Finished Products Depending on the type of dosage form, the SU should provide relevant information on physical properties of excipients to the RU, including:

- definitive form (for solid and inhaled dosage forms);
- solubility profile (for solid, inhaled and transdermal dosage forms);
- partition coefficient, including the method of determination (for transdermal dosage forms);

- intrinsic dissolution rate, including the method of determination (for transdermal dosage forms);
- particle size and distribution, including the method of determination (for solid, inhaled and transdermal dosage forms);
- bulk physical properties, including data on bulk and tap density, surface area and porosity as appropriate (for solid and inhaled dosage forms);
- compaction properties (for solid dosage forms);
- melting point range (for semi-solid/topical dosage forms);
- pH range (for parenteral, semi-solid/topical, liquid and transdermal dosage forms);
- ionic strength (for parenteral dosage forms);
- specific density/gravity (for parenteral, semi-solid/topical, liquid and transdermal dosage forms);
- viscosity and/or viscoelasticity (for parenteral, semi-solid/topical, liquid and transdermal dosage forms);
- osmolarity (for parenteral dosage forms);
- water content and determination of hygroscopicity, including water activity data and special handling requirements (for solid and inhaled dosage forms);
- moisture content range (for parenteral, semi-solid/topical, liquid and transdermal dosage forms);
- microbiological considerations in accordance with regional pharmacopoeial requirements (for parenteral, semi-solid/topical, liquid, inhaled and transdermal dosage forms); and
- information on adhesives supporting compliance with peel, sheer and adhesion design criteria (for transdermal dosage forms).

Packaging

- Information on packaging to be transferred from the SU to the RU include specifications for a suitable container/closure system, as well as any relevant additional information on design, packing, processing or labeling requirements needed for qualification of packaging components at the RU. For quality control testing of packaging components, specifications should be provided for drawings, artwork, material.

Documentation: The documents used in technology transfer are presented in table 1.

Table 1. Documentation for transfer of technology (TOT)

Key task	**Documentation provided by SU**	**Transfer documentation**
Project definition	Project plan and quality plan (where separate documents), protocol, risk assessments, gap analysis	Project implementation plan **TOT protocol**
Quality agreement Facility assessment	Plans and layout of facility, buildings (construction, finish) Qualification status (DQ, IQ, OQ) and reports	Side-by-side comparison with RU facility and buildings; gap Analysis **Qualification protocol and report**
Health & Safety assessment	Product-specific waste management plans Contingency plans	
Skill set analysis and training	SOPs and training documentation (product-specific operations, analysis, testing)	Training protocols, assessment results
Analytical method transfer	Analytical method specifications and validation, including in-process quality control	Analytical methods transfer protocol and report
Starting material Evaluation Equipment selection and transfer	Specifications and additional information on APIs, excipients Inventory list of all equipment and systems, including makes, models, qualification status (IQ, OQ, PQ). Drawings, manuals, logs, SOPs (e.g. set-up, operation, cleaning, maintenance, calibration, storage)	Side-by-side comparison with RU equipment (makes, models, qualification status) Gap analysis. **Qualification and validation protocol and report**
Process transfer: manufacturing and packaging	Reference batches (clinical, dossier, bio-batches) Development report (manufacturing process rationale),History of critical analytical data Rationale for specifications, Change control documentation, Critical manufacturing process Parameters Process validation reports Drug master file. API validation status and report(s) Product stability data Current master batch manufacturing and packaging records List of all batches produced Deviation reports, Investigations, complaints, recalls Annual product review	History of process development at RU, Experiences at RU should be recorded for future reference Provisional batch mfg document (RU to develop) Provisional batch packaging document (RU to develop) Description of process at RU (narrative, process map, fl ow chart) **Process validation protocol and report**
Cleaning	Cleaning validation, Solubility information; therapeutic doses; category (toxicology); existing cleaning SOPs; validation reports chemical and micro; agents used; recovery study	Product- and site-specifi c cleaning SOPs at RU **Cleaning validation protocol and report**

Premises and Equipment

Premises

- The SU should provide information to the RU on the layout, construction and finish of all buildings and services (heating, ventilation and air-conditioning (HVAC), temperature, relative humidity, water, power, compressed air) impacting the product, process or method to be transferred.
- The SU should provide information on relevant health, safety and environmental issues, including:
- inherent risks of the manufacturing processes (e.g. reactive chemical hazards, exposure limits, fire and explosion risks).
- health and safety requirements to minimize operator exposure (e.g. atmospheric containment of pharmaceutical dust).
- Differences in building, construction layout and services between the SU and the RU should be listed and compared in view of the following considerations:
- buildings and services at the RU should be capable of accommodating the product, process or method under transfer to the agreed quality standard and production volume in compliance with GMP;

DQ, design qualification; IQ, installation qualification; OQ, operational qualification; API, active pharmaceutical ingredient; SOPs, standard operating procedures; RU, receiving unit.

- quality control laboratories should be equipped and capable of testing all APIs, excipients, intermediate and finished products, packaging components and cleaning validation samples;
- buildings intended for production of a highly sensitizing nature (e.g. penicillins and cytotoxic materials) should be dedicated for this purpose and located in a different facility from other production units; and
- health, safety and environmental issues, including waste management, emergency planning, minimization of operator exposure and environmental impact, should be addressed at the RU in compliance with any regulatory or company-developed rules, regulations and limits.

Equipment

The SU should provide a list of equipment, makes and models involved in the manufacture, filling, packing and/or control of the product, process or method to be transferred, together with existing qualification and validation documentation. Relevant documentation may include:

- drawings;
- manuals;
- maintenance logs;
- calibration logs; and
- SOPs (e.g. equipment set up, operation, cleaning, maintenance, calibration, storage).

The RU should review the information provided by the SU together with its own inventory list including the qualification status (IQ, OQ, PQ) of all equipment and systems, and perform a side-by-side comparison of equipment at the two sites in terms of their functionality, makes, models and qualification status.

Based on the side-by-side comparison, the RU should perform a gap analysis to identify requirements for adaptation of existing equipment, or acquisition of new equipment, to enable the RU to reproduce the process being transferred. GMP requirements should be satisfied, and intended production volumes and batch sizes (e.g. same, scaled-up or campaign) should be considered. Factors to be compared include:

- minimum and maximum capacity;
- material of construction;
- critical operating parameters;
- critical equipment components (e.g. filters, screens, temperature/pressure sensors); and
- range of intended use.

The facility- and building-specific location of all equipment at the RU should be considered at the time of drawing up process maps or flow charts of the manufacturing process to be transferred, including movement of personnel and material.

The impact of manufacturing new products on products currently manufactured with the same equipment should be determined.

Where existing producing equipment needs to be adapted to be capable of reproducing the process being transferred, a detailed development project should be included in the transfer protocol.

New equipment should be designed and constructed to facilitate the process and ease cleaning and maintenance operations. Any newly acquired equipment should undergo a qualification protocol up to and including OQ level.

Applicable operating procedures for set-up, operation, cleaning, storage and maintenance should be developed by the conclusion of OQ. Supporting documents such as drawings of equipment and piping installations, manuals, maintenance logs and calibration logs should be retained.

Qualification and Validation

General

- ✓ Qualification and validation of facilities, equipment, systems and procedures are essential to demonstrate that all critical stages of the transfer project have been completed successfully, enabling the RU to reproduce the product, process or method routinely to the specifications agreed with the SU.
- ✓ Validation performed as part of the transfer project should be documented in a validation master plan (VMP). The VMP should identify the stages which need to be validated and define acceptance criteria.
- ✓ For intra-company transfers, the RU should operate under the same VMP as the SU. For inter-company transfers, a VMP should be in place at the RU before the transfer.
- ✓ The RU should prepare a validation protocol (VP) for each sequential step. Successful execution of each VP should be documented in a validation report (VR).
- ✓ Setting up and commissioning of systems at the RU need to be completed before qualification and validation can be performed at the RU. The steps required for this purpose have been described in this guideline for buildings, services and equipment, manufacturing, packaging and cleaning and analytical testing. In brief, the following basic steps apply equally to each of these areas:
    - the SU should provide information on materials, systems and procedures involved in the manufacturing of the product, process or method to be transferred;
    - the RU should review the information provided by the SU, and audit its current systems, equipment and processes, including non-process related practices and support services that impact the process;

- based on this review, the RU should either accept the information provided or develop it further to prepare site-specific procedures, SOPs, training programmes and protocols which will form the basis of the qualification and validation; and
- relevant staff, e.g. operators and analysts, should be trained in any new processes as required.

✓ Once the required systems and procedures have been commissioned at the RU, and successful training has been documented, qualification and validation of facility and equipment should be executed, followed by validation of analytical test methods, process validation for manufacturing and packaging, and cleaning validation.

✓ The RU should review the gap analysis and prepare, where appropriate, VPs for the facility, services and equipment.

✓ Both new and existing equipment should satisfy the VPs associated with purchase and design specifications, factory acceptance tests (FAT) if possible, IQ and OQ.

✓ Performance qualification, including a further assessment of operating parameters with relation to product characteristics, should be established on commencement of trial batches.

✓ Successful completion of qualification and validation should be documented in a report.

Quality Control:

Transfer of analytical methods should accommodate all the analytical testing required to demonstrate compliance of the product to be transferred with the registered specification.

Transfer of analytical methods used to test pharmaceutical products, their ingredients and cleaning (residue) samples, needs to be in place before process validation studies of manufacturing operations can be carried out.

The SU should prepare a protocol defining the steps to be undertaken for analytical method transfer. The analytical methods transfer protocol should describe the objective; scope; responsibilities of the SU and the RU; materials, methods and equipment; the experimental design and acceptance criteria; documentation (including information to be supplied with the results, and report forms to be used if any); deviations; references; signed approval; and details of reference samples (APIs, 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;
- provide acceptance criteria and validation protocols for any RU training exercises;

- assist in analysis of quality control testing results;
- define and justify all methods to be transferred for testing a given product, ingredient or cleaning sample;
- define experimental design, sampling methods and acceptance criteria;
- provide any validation reports for methods under transfer, and demonstrate their robustness;
- provide data for the equipment used and any standard reference samples; and
- provide approved SOPs used in testing.

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 quality control is available and qualified at the RU site. Equipment should be replicated where possible, but it is accepted that different models, e.g. spectrometers and chromatographs, could already be in place;
- ensure that adequately trained and experienced personnel is in place for analytical testing;
- provide a documentation system capable of recording receipt and testing of samples.

A suggested analytical training protocol would be as follows:

- SU and RU analysts assay two retained samples from SU;
- SU and RU analysts then assay two sub-potent samples (available from SU or spiked);
- SU and RU analysts assay samples taken from RU production;
- RU analyst provides sufficient replicate analyses to enable a significance test (e.g. student's *t*) against the established method at the SU site; and
- a similar exercise should be undertaken for analysis of low levels of APIs.
- All training activities and outcomes should be documented.

Analytical methods Transfer

The analytical methods transfer protocol should cover the following sections:

- objective;
- scope;
- responsibilities of the SU and the RU;
- materials, methods and equipment;
- the experimental design and acceptance criteria;

- documentation (including information to be supplied with the results, and report forms to be used if any);
- deviations;
- references;
- signed approval; and
- details of reference samples (APIs, intermediates and finished products).

Successful transfer and validation of analytical methods should be documented in a report.

Approved regulatory bodies and agencies

The principal regulatory bodies entrusted with the responsibility of ensuring the approval, production and marketing of quality drugs in India at reasonable prices are:

- ✓ ***The Central Drug Standards and Control Organization (CDSCO),*** located under the aegis of the Ministry of Health and Family Welfare. The CDSCO prescribes standards and measures for ensuring the safety, efficacy and quality of drugs, cosmetics, diagnostics and devices in the country. Regulates the market authorization of new drugs and clinical trials standards; supervises drug imports and approves licences to manufacture the above-mentioned products.
- ✓ ***The Drugs Controller General of India (DCGI),*** With respect to licencing and quality control issues, market authorization is regulated by the Central Drug Controller, Ministry of Health and Family Welfare, Department of Biotechnology, Ministry of Science and Technology (DST) and Department of Environment, Ministry of Environment and Forests. State drug controllers have the authority to issue licences for the manufacture of approved drugs and monitor quality control, along with the ***Central Drug Standards Control Organization (CDSCO).***
- ✓ ***The Food and Drug Administration (FDA or USFDA)*** is a federal agency of the United States Department of Health and Human Services, one of the United States federal executive departments. The FDA is responsible for protecting and promoting public health through the Control and supervision of food safety, tobacco products, dietary supplements, prescriprion and over the counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical, electromagnetic radiation emitting devices (ERED), cosmetics, animal foods & feed[4] and veterinary products.
- ✓ ***The Therapeutic Goods Administration (TGA)*** is part of the Australian Government Department of Health, and is responsible for regulating therapeutic goods including

prescription medicines, vaccines, sunscreens, vitamins and minerals, medical devices, blood and blood products. Almost any product for which therapeutic claims are made must be entered in the Australian Register of Therapeutic Goods (ARTG) before it can be supplied in Australia.

- ✓ ***Medicines and Healthcare products Regulatory Agency (MHRA)*** regulates medicines, medical devices and blood components for transfusion in the UK.

Commercialization - practical aspects and problems (case studies)

Technology transfer are discussed with certain practical studies.

Case Study 1 The blending of drug with excipients is presented in table 2. [3]

Factors considered in the proposed technology transfer (scale up)

Geometric Similarity: Ratio of all lengths constant (constant fill ratio)

Dynamic Similarity: Maintenance of Forces (Froude number)

Kinematic Similarity: Maintaining a consistent number or revolutions

Table 2, Scale-up in QbD Approach: Blending

Scale	Amount (kg)	Blender Capacity	Blending Speed (rpm)	Blending Time (min)	Nrev	Volume Fill Ratio (%)
Laboratory	2	8 qt	25	12	300	~50
Pilot	40	7.5 cu.ft	15	20	300	~50
Commercial	180	30 cu. Ft	10	30	300	~50

Conclusion of case study 1: The desired content uniformity was attained by modifying the above parameters such as blending speed and blending time.

Case Study 2 (Drug layering on MCC spheres) [3]

Equipment of production having greatest similitude (geometric) to the intended to commercial scale process, similar particle trajectories and dynamics enables maintenance of process parameters through scale-up with the exception of air-flow which is linearly scaled (Figure 3, Table 3).

Conclusion of case study 2

Air flow rate and total spray rate were adjusted to obtain uniform coating of drug on MCC spheres. Assay of the formulation was 99.9% in both pilot batch and commercial batch.

Table 3, Parameters for pilot and verification batches at commercial scale

	Pilot batches	**Commercial scale**
Starting Batch Size	40 kg	140 kg
Ending Batch Size	56 kg	198 kg
Estimated use of capacity	50%-70%	56%-79%
Number of Partition(s)	1	3
Partition height	30-50 mm	30-50 mm
Nozzle	1.2 mm	1.2 mm
Product Temperature	44-48 C	44-48 C
Air Flow Rate	**810±90 cfm**	**2430±270 cfm**
Spray Rate per nozzle	135±25 g/min	135±25 g/min
Total Spray Rate	**135±25 g/min**	**405±75 g/min**
Atomization Pressure per nozzle	2.5-2.9 bar	2.5-2.9 bar

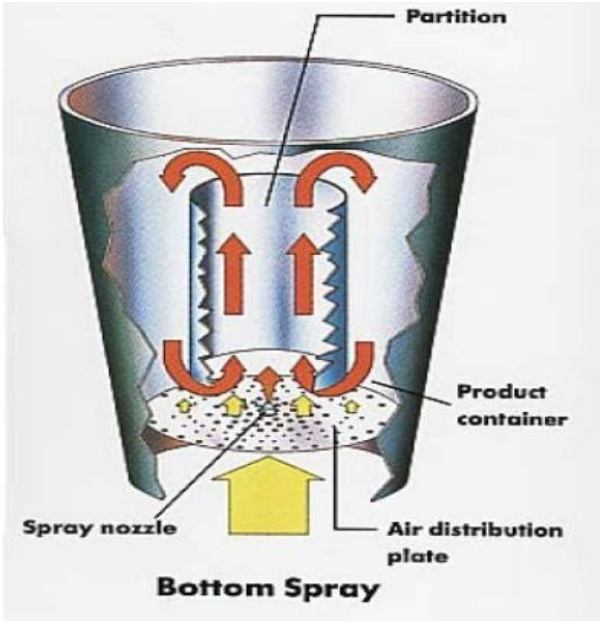

Figure 3A Pilot Scale Studies (40 kg each) using 18'' Wurster HS insert

Figure 3B Commercial Scale (140 kg) using 32'' Wurster HS insert

TT agencies in India - APCTD, NRDC, TIFAC, BCIL, TBSE /SIDBI [4]

Asian and Pacific Centre for Transfer of Technology (APCTT)

• It is a United Nations Regional Institution under the Economic and Social Commission for Asia and the Pacific (ESCAP) established in 1977 in Bangalore, India. In 1993, the Centre moved to New Delhi, India. APCTT promotes transfer of technology to and from small- and medium-scale enterprises (SMEs) in Asia and the Pacific. APCTT implements development projects funded by international donors aimed at strengthening the environment for technology transfer among SMEs. The objective of APCTT is to strengthen the technology transfer capabilities in the region and to facilitate import/export of environmentally sound technologies to/from the member countries.

National Research Development Corporation (NRDC)

- National Research Development Corporation (NRDC) was established in 1953 by the Government of India, with the primary objective to promote, develop and commercialise the technologies / know-how / inventions / patents / processes emanating from various national R&D institutions / Universities and is presently working under the administrative control of the Dept. of Scientific & Industrial Research, Ministry of Science & Technology. During the past six decade of its existence and in pursuance of its corporate goals, NRDC has forged strong links with the scientific and industrial community in India and abroad. It is recognized as a large repository of wide range of technologies spread over almost all areas of industries, viz. Agriculture and Agro-processing, Chemicals including Pesticides, Drugs and Pharmaceuticals, Bio Technology, Metallurgy, Electronics and Instrumentation, Building Materials, Mechanical, Electrical and Electronics etc. It has licensed the indigenous technology to more than 4800 entrepreneurs and helped to establish a large number of small and medium scale industries. NRDC also undertakes number of activities such as meritorious inventions awards, Techno-Commercial support, Technical and financial assistance for IPR Protection, Value addition services and support for further development of technologies and much more.

Technology information, Forecasting and assesmement Council (TIFAC)

- TIFAC is an autonomous organization set up in 1988 under the Department of Science & Technology to look ahead in technology domain, assess the technology trajectories, and support innovation by networked actions in selected areas of national importance TIFAC embarked upon the major task of formulating a Technology Vision for the country in various emerging

technology areas. Under the leadership of Dr. APJ Abdul Kalam, Technology Vision 2020 exercise led to set of 17 documents, including sixteen technology areas and one on services. In more than 25 years of its service to the nation, it has delivered number of technology assessment and foresight reports. While inaugurating the 103rd Indian Science Congress in Mysuru, Hon'ble Prime Minister of India Shri Narendra Modi released the Technology Vision 2035 prepared by TIFAC.This is being followed by release of Technology Roadmaps in 12 thematic areas of national priorities and importance • Education, Medical Science & Health Care, Food and Agriculture, Water, Energy, Environment, Habitat, Transportation, Infrastructure, Manufacturing, Materials and Information & Communication Technologies (ICT).

Biotech Consortium India Limited (BCIL)

Biotech Consortium India Limited (BCIL), New Delhi was incorporated as public limited company in 1990 under The Companies Act, 1956. The consortium is promoted by the Department of Biotechnology, Government of India and financed by the All India Financial Institutions and some corporate sectors BCIL 's major functions include the development and transfer of technology for the commercialisation of biotechnology products, project consultancy, biosafety awareness and human resource development BCIL has been successfully managing several Flagship schemes and Programmes of the Department of Biotechnology, Government of India. Most notable include Biotechnology Industry Partnership Programme, 2. Biotechnology Industrial Training Programme and Small Business Innovation Research Initiative

Technology Bureau for Small Enterprises (TBSE)/ Small Industries Development Bank of India (SIDBI).

- The Technology Bureau for Small Enterprises (TBSE) is a platform for MSMEs to tap opportunities at the global level for the acquisition of technology or establishing business collaboration. TBSE is a result of the cooperative initiative of the United Nations' Asian and Pacific Centre for Transfer of Technology (APCTT) and Small Industries Development Bank of India (SIDBI) in 1995. TBSE also receives partial funding from the Office of DC (SSI), Government of India. Features of TBSE Offering a professionally managed system for the reasons of technology and collaboration exploration helping in the building up of confidence between potential partner. It providing an opportunity to global technology market through the

process of networking. Taking up project appraisal and the preparation of a business plan. The new technologies for the reason of transfer are sourced from countries namely China, Philippines, South Korea, Australia, Germany, as well as the U.S.

TT related documentation - confidentiality agreement, licensing, MoUs, legal issues. [5]

Confidentiality Agreements

The aim of a confidentiality agreement is to protect all information of party entering negotiations. Before any concrete negotiations on the transfer of a technology can really start all parties involved must be able to evaluate the technology offered. Both the technological and the commercial possibilities of the offer will thereby be taken into account. Before giving anybody access to your technology a confidentiality agreement should be drafted with discussion on the main topics to be addressed in such agreement keeping in mind that all the standard clauses of an agreement should also be included (parties, term and termination, applicable law). The first item in any confidentiality agreement should be a brief but clear description of the technology that will be transferred. What are the main specifications of this technology and what is its relevant application? In this same disposition of the agreement a reference to the property rights of the party offering can be made.

Licensing

The legal core of the transfer of technology is constituted by a licensing agreement. By signing this agreement the owner of a technology, the licenser, gives the right to another company, the licensee, to make use of this technology. A licence does not alter the property rights of the owner: he remains the only proprietor of the technology. He could also sell his technology whereby the buyer becomes the owner and replaces the seller. But if an owner of a technology prefers to enter into an agreement with a licensee he will give him limited rights. The licensee cannot dispose of the technology but he can use it. This use will be more or less limited. A limitation in time, in geographical market, in product market or in the application can be introduced in a licence. The licence will determine the relationship between the licenser and licensee for the whole duration of their co-operation and a lot of questions will have to be answered before this relationship can start.

Memoranda of Understanding (MOUs)

Often collaborative research efforts with outside institutions are defined in Memoranda of Understanding (MOU) before other agreements are executed. An MOU typically defines how

intellectual property will be shared and the roles and responsibilities of the involved parties. If you are planning to enter into a collaborative relationship with an outside party, it is important to discuss the possibility of an MOU. Office of Technology Commercialization is responsible for drafting MOUs related to collaborative research. MOUs typically identify a lead institution for managing intellectual property and provide details on how licensing income will be shared.

Legal Issues

The following types legal issues are generally observed in technology transfer.

- Legal contractual agreements
- Tax implications
- Legal issues in intellectual property transaction
- Problems associated with IPR litigation
- Legislations covering IPRs in India

References

1. WHO Technical Report Series, Annex 7, No. 961, 2011.

2. Guidance for Industry Q10 Pharmaceutical Quality System. U.S. Department of Health and Human Services Food and Drug Administration, ICH, April 2009.

3. Raw AS. QbD Scale-up Considerations Linking Exhibit Batches to Commercial Production. GPhA/FDA Quality by Design Workshop for ANDAs, FDA – CDER - Office of Generic Drugs, May 5, 2011.

4. Dave V, Pareek A, Yadav S, Sharma S, Paliwal S. Pharmaceutical industry and technology transfer agencies in India. The Pharma Review, jan-Feb, 2013, 116-112.

5. Dogra R, Garg R and Jatav P. Technology Transfer in Pharmaceutical Industry: Transfer of Process from Development to Commercialization. IJPSR, 4(5), 2013, 1692-1708.