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Review Article

Technology transfer in pharmaceutical industry- A Review

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Abstract

The objective of this review article is to study how technology is transferred in pharmaceutical industry. The article attempts to discuss about the technology transfer process, importance of technology transfer, reasons for using technology transfer, policy approaches of technology transfer, effective factors in technology transfer, Facets of technology transfer, goals of technology transfer, steps involved in technology transfer, barriers of technology transfer and the issues involved in the technology transfer in the pharmaceutical industry and understand the aspects related with technology transfer.

Keywords: Technology transfer, Steps involved, Barriers, policy approaches.

1. Introduction

A proper technology transfer (TT) is both essential and important to drug discovery and development for new medicinal products. It is also required to upgrade drug quality planned during research development and to final product during manufacturing as well as to guarantee that stable quality is transferred.

According to WHO, 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. 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.

Technology transfer (TT) is defined as "the transfer of the manufacturing process for a new pharmaceutical Drug Substance (DS) and Drug Product (DP), respectively, from the transferring site (in this case R&D) to the receiving site or designated commercial manufacturing site." This includes all the associated knowledge, information and skills to be able to manufacture the DS and DP at the receiving site.

The development and transfer of knowledge and technology has been and will continue to be critical to success in pharmaceutical industry. The transfer of technology is considered as both fundamental and significant to the drug discovery and development process for any new medicinal entity. This process is important for to elucidate necessary information for technology transfer from R & D (Research &Development) to PDL (product development laboratory). This review gives a brief description about the importance, objective, Factors, steps in technology transfer, various cases and barriers by which technology transfer takes place.

Why technology transfer is required in Pharmaceutical Industry [2]

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 or it is the process bywhich a developer of technology makes its technology available to commercial partner that will exploit technology. In pharmaceutical industry preparation of dosage form needs scale up at several stages, such as small scale laboratory development from 0.5-2kgbatch can be scaled up to 5-10 kg and then to20-100 kg on a pilot scale. Production scale can typically range from 200 kg to greater than 1000kg. Technology transfer involves manufacturing drug product with increasing batch sizes on larger equipment or using continuous processing on pilot scale equipment. Generally scale up involves the transfer of technology and the transfer of knowledge that has been accumulated during the small scale development of product and processes. It is important to realize that good communication is critical for formulation and process transfer to be successful. It is essential for a researcher or developer of technology to make available this technology to another person's to exploit for the progress of development of technology and for exploitation of a technology in different fields of applications and to make is use with another organization that may have better manufacturing capability, marketing capability and commercial capability. In the pharmaceutical industry, technology transfer by collaborating with other departments and other organizations to commercialize a pharmaceutical product is a common process.

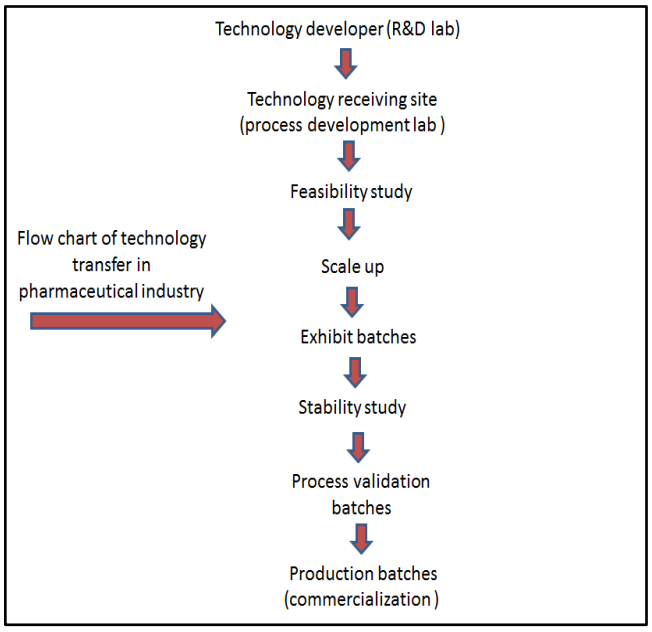

Figure 1: Flow chart of technology transfer in pharmaceutical industry [3]

1.1 Importance of Technology Transfer in Pharmaceutical Industry [4, 15]

- To elucidate necessary information to transfer technology from R&D to actual manufacturing by sorting out various information obtained during R&D;
- To elucidate necessary information to transfer technology of existing products between various manufacturing places;
- To exemplify specific procedures and points of concern for the two types of technology transfer in the above to contribute to smooth technology transfer. This is applies to the technology transfer through R&D and production of drug substances or drug products and the technology transfer related to post-marketing changes in manufacturing places.

1.2 Reasons for technology transfer [5, 15]

1) Lack of manufacturing capacity: The developer of technology may only have manufacturing equipment which is suitable for small scale operation, and must collaborate with another organization to do large scale manufacturing.
2) Lack of resources to launch product commercially: The original inventor of technology may only have the resources to conduct early-stage research such as animal studies and toxicology study, but doesn't have the resources to take technology through its clinical and regulatory phases.
3) Lack of marketing and distribution capability: The developer of technology may have fully developed the technology and even have obtained regulatory approvals and product registrations, but it may not have the marketing and distribution channels.
4) Exploitation in a different field of application: Each partner may have only half of the solution i.e. the developer of the technology might be capable of exploiting the technology itself in the field of diagnostic applications and may grant exploitation right to commercial partner for the exploitation of therapeutics application.

1.3 Technology transfer policy [6]

A pharmaceutical technology transfer can be defined as the transfer of scientific information, a capability or a technological basis associated with a drug or a pharmaceutical procedure from a donor side (knowledge centre) to a receptor side (drug manufacturing plant)implying a positive experience learned and realized by both sides and complying all the regulatory requirements in terms of Efficacy, Quality and Safety. Thus the concept of outsourcing and externalization comes into play as an opportunity entailing the delegation of activities out of the company as well as cessation of human resources and materials.

This concept or necessity is supposed to respond to a series of weak points concerning drug development strategies and to be either reinforced locally or outsourced like these;

- Development management structure proves insufficient. No management educational plans in executive teams
- Lack of equipments and infrastructure. Poor confidence in R & D know-how
- Lack of introduction of Good Laboratory Practices, GLP, & Good Manufacturing Practices, GMP, guidelines and other quality systems. Realization of uncontrolled trials and lack of pilot trials
- Dispersion of the research effort. Lack of focusing objectives and establishing merge ring and joint venture strategies
- Updating and universalization of the resources available for all researchers. Lack of motivation and flexibility of researchers
- Lack of communication with the regulatory authorities.

Exceptional search of local and regional opportunities. On the other hand, the degree of outsourcing of development activities depends on the company's strategy.

The transfer of technology from a development unit (donor side) and its subsidiary companies, licensed ones, subcontracted ones or simply clients (receptor side) aims at the supply of information and methods enabling the receptor side to start the production of a new product, bulk ware or finished drug.

Formalizing the technology transfer policy can be expected:

- The objectives of the company and business are kept
- A positive impact on the quality of the product in question is produced
- The introduction of new products in the market is facilitated
- The compliance with the regulatory requirements is assured
- The costs are reduced

By other hand, the drug production facilities are concerned by technology transfer as they are increasing their production capacities working for other companies.

This implies an excellent opportunity for companies with either low used installations or equipments with a degree of exploitation of not more than 50 % of their maximum capacity or specialized companies with own procedures and technologies covering market gaps.

1.4 Effective factors in technology transfer [7]

"Technology transfer can be considered successful if a Receiving Unit can routinely reproduce the transferred product, process or method against a predefined set of specifications as agreed with a Sending Unit or Development Unit"

Main factors that affect the process of technology transfer in pharmaceutical industry are as follows:

1) Investment in Research and Development.
2) Establishing relationship between production and research.
3) Information development in the field of technology transfer methods.
4) Organizational, Equipmental and Informational infrastructures.
5) Employment of International specialist in the field of technology and creation of appropriate relationship between recipient and sender technology.
6) Awareness of fundamental and important factors required for technology transfer.
7) Consideration of existing and old technologies.
8) Degree of development and improvement of technology on the basis of internal resources.

2. Facets of technology transfer [8]

a. Govt. labs to private sectors

This type of Technology Transfer is advantageous as the Govt. labs can get good financial support and funds from the govt. for their research work and the technology developed by them reaches the private sector.

b. Between Private sectors of same country

This type of Technology Transfer generally occurs due to lack of appropriate financial resources or inadequate knowledge of regulatory requirements, thus the private sector that develops the technology is paid by other sector that absorbs the technology.

c. From Academics to private sectors

Academic sectors that are actively involved in research develop the technology and make it available to private firms. By collaboration of private firms with the institutions, money can be saved.

d. Between Academy, Private and Govt. sectors

In this type of Technology Transfer govt. provides necessary funds to the academic institutions in developing technology that can be transferred to the industry.

3. Goals of technology transfer [9]

According to ICH Q10 guidelines

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 realization. This knowledge forms the basis for the manufacturing process, control strategy, process validation approach and on-going continual improvement.

- Is a valuable step in the developmental life cycle leading to successful commercial manufacturing?
- To take all the gathered knowledge and use it as the basis for the manufacturing control strategy, the approach to process qualification and on-going continuous improvement.
- The transition of the product/process/analytical method knowledge between development and manufacturing sites.
- To ensure variability of process and parameters are controlled and sufficient in the face of the rigors of a commercial production environment. To verify parameters established during development are still within the determined design space and adjusted at scale-up.

4. Steps in technology transfer [10-12, 15]

Technology Transfer is not a single way process. Whether a tablet, a Transdermal patch, a topical ointment, or an injectable, the transformation of a pharmaceutical prototype into a successful product requires the cooperation of many individuals.

The classic view of a flow from basic to applied technology is a great oversimplification-sometimes, e.g. problems or insights arising at the production level give rise to new ideas that contribute to fundamental basic advance. At least in some sectors, close links between the basic researchers and manufacturing experts, and even marketing personnel contribute to competitiveness and advancement.

During development of a formulation, it is important to understand procedure of operations used, critical and non-critical parameters of each operation, production environment, equipment and excipient availability, which should be taken into account during the early phases of development of formulation, so that successful scale up can be carried out. Appropriate care during technology transfer is important to enhance drug quality as developed by R & D in final formulation as well as to assure quality for predetermined period of time. The various steps involved in technology transfer are given below:

A. Development of technology by R & D [Research Phase]
B. Technology transfer from R&D to production [Development Phase]
C. Optimization and Production [Production Phase]

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

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. For this different test and compatibility studies are done.

b. Identification of specification and quality by R&D

Generally it should be considered by R & D the quality of product should meet the specifications of an innovator product. For this different stability studies are carried out for innovator product and for product which is to be manufactured.

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

R&D provides technology transfer dossier (TTD) document to product development laboratory which contains all information of formulation and drug product as given below.

Technology Transfer Dossier (TTD): TTD contained all the information of drug product as given below:

- Master formula card (MFC)
- Master Packaging Card (MPC)
- Master formula
- Standard Test Procedures
- Specifications
- Development report
- Packaging development report

Master formula card (MFC): MFC included Product name along with its Strength, Generic name, MFC number, Page number, Effective date, shelf life, market, packaging details, storage conditions, precautions for personnel safety as well as for the product safety. Ingredients details with pharmacopoeial status along with the specifications numbers, brand names / grades along with approved vendors label claim and a brief manufacturing detail

Masters packaging card: It gives information about packaging type, material use for packaging, stability profile of packaging and shelf life of packaging.

Master formula: It describes formulation order and manufacturing instruction. Formulation order and manufacturing instruction gives idea of process order, environment condition required and manufacturing instruction for dosage form development.

Specification and standard test procedure (STPs): It helps to know active ingredients and excipients profiles, in process parameter and specification, product release specification and finished product detail.

Research for factory production: To manufacture drugs with qualities as designed, it is required to establish appropriate quality control method and manufacturing method, after detecting variability factors to secure stable quality in the scale up validation that is performed to realize factory production of drug designed on the basis of result from small-scale experiments.

Consistency between quality and specification: When product specification is established on the basis of the quality of product determined in the above, it is required to

verify that the specification adequately specifies the product quality. In short, the consistency between quality and specification is to ensure in the products specification that the quality predetermined in the quality design is assured as the manufacture quality and the product satisfies the quality of design.

Assurance of consistency through development and manufacturing: To make developed product have indications as predetermined in clinical phases, quality of design should be reproducible as the quality of product (assurance of consistency). For this purpose transferring party in charge of development should fully understand what kind of technical information is required by the transferred party in charge of manufacturing and should establish an appropriate evaluation method to determine whether a drug to be manufactured meets the quality of design.

C) Production Phase (Optimization and Production)

a. Val idation studies

Production is implemented after various validation studies verify that, it is able to consistently manufacture product based on transferred manufacturing formula with a higher degree of stability. Research and development department transferring technology should take responsibility for validation such as performance qualification, cleaning validation and process validation unique to subject drugs.

b. Scale-up for production

Scale up involves the transfer of technology during the small scale development of the product and processes. It is essential to consider the production environment and system during development of process. Different operations e.g. dispensing, sifting, blending, compaction/dry granulation/wet granulation, compression, coating are used in the formulation of solid dosage form. From blending to film coating, each process is easy for pharmaceutical professionals to be absorbed in the particular part of the manufacturing process for which they are directly responsible. Operators concentrate on keeping their segment of the production process running smoothly. But the whole manufacturing line can be improved, even before production begins, if technology transfer is implemented thoughtfully. Effective technology transfer helps to provide process efficiency and control and maintain product quality.

c. Considerations of different parameters for scale-up:

Before starting scale-up, we also considered different parameters that should be optimum for successful technology transfer. These were: Flexibility, Cost, Dependability, Innovation and Product Quality. It was important to realize that good communication was critical for formulation and process transfer to be successful.

d. Selection of method:

The method for batch fabrication was selected on the basis of data given from R&D. Granulation, blending; compression and coating were critical parameters for technology transfer.

D) Technology Transfer Documentation [13, 15]

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 importanttests such as contents impurities and dissolution.
(7) Verifications of results.

(b) Technology Transfer Plan

The technology transfer plan is to describe itemsand contents oftechnology to be transferred and detailed procedures of individual transfer and transfer schedule, establishjudgment criteria for the completion of the transfer. The transferring party should prepare the plan beforethe 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 takenaccordingly to thetechnology plan and are evaluated to confirm that the predeterminedjudgment criteria are met. Bothtransferring and transferred parties should document thetechnology transfer report.

E) Exhibit

After taking scale up batch of the product, manufacturing of exhibit batches take place. In case of exhibit, batch sizes are increased along with equipment and their process is involved. They are done for filing purposes in different regulatory agencies.

5. Barriers of Technology Transfer [7]

- Lack of market share: Local producers face significant challenges in meeting international Quality standards and capturing a critical market share. Greater market share would increase profitability.
- Cost of prequalification: There is benefit in meeting international standards since it opens up the opportunity for trading across the entire world.
- Labour issues: The pharmaceutical sector demands relatively skilled labour. High labour turns over and absenteeism owing to unattractive conditions of service is negative contributor.
- Unsuccessful or incomplete Process Validation.
- High rates of batch rejections, excessive labour requirements, increased cost of product etc.
- Incomplete Documentation.
- Product does not show specifications as intended.
- Delayed regulatory approval and/or product launch

6. Few cases of technology transfer [14]

The process of Technology Transfer is actively being pursued in India through Government laboratories, Academics Institutions and Commercial entities.

1. **The Bhabha Atomic Research Centre (BARC),** has developed and transferred around 90 technologies in the areas such as environment and health; electronics; electrical and mechanical; chemical and metallurgy; radioisotope and applications.

2. The National Chemical Laboratory (NCL) Pune, has several linkages with universities and pharmaceutical industries to ensure successful scale up and implementation of technology.

3. Department of Biotech (DBT) has successfully transferred some techniques of forest trees through tissue culture.

4. Eli Lily has entered in technology transfer agreement with Shasun Chemicals and Drugs for the manufacturing of anti T.B drug CYCLOSERINE produced by shasun to meet Eli Lily global demand.

7. Organization of technology transfer [9]

As the team concept is always the best approach to achieve a successful technology transfer projects. The core technology transfer team must be commissions immediately following the decisions of the executive management to pursue the drug candidate to commercialization. A typical technology transfer core team will likely be comprised of individual's representives of the different segments of the business.

1) The Project Manager- The overall coordination, responsibility and communication progress to the management. His or her role may be enhanced as necessary by the additional staff and responsibility and authority delegated as appropriate.
2) Regulatory Affairs- For the coordination of the appropriate regulatory filings, advice on the timing of approval, filing documentation contents and response to the regulatory inquiries.
3) Engineering- For coordination of associated capital projects and direct and equipment acquisition, control the construction, installation and qualification.
4) The Material management- Those units responsible for strategic planning, pure chasing, supply chain activities and resource allocation are included. These members will analyse and recommend the most favourable manufacturing strategy in consideration of partnership in business, internal capability, and advantages of tax for the corporation.
5) The Manufacturing operations- Receiving location of production activities and to represent the originating site. These representatives should have the sufficient authority to commit the necessary personal and plant resource to achieve the project within the defined time and cost limitations.
6) Research and Development [R&D]- To support the technical issues and resolve problems. This group provides the expertise process and would expect to direct and train the production trials at the receiving site.

7. Conclusion

Effective technology transfer is critical to success in pharmaceutical industry. In pharmaceutical industry technology transfer can be defined as the transfer of scientific information, a capability or a technological basis associated with a drug or a pharmaceutical procedure from a donor side (knowledge center) to a receptor side (drug manufacturing plant) implying a positive experience learned and realized by both sides and complying all the regulatory requirements in terms of Efficacy, Quality and Safety. A healthy communication between different countries and different organizations are the key to the success of Technology transfer and development. So, the knowledge and information should be transferred equally and continuously from transferring party to the transferred party, this will help in the product manufacturing process and thus the development of both the parties.

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