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Review article

Technology transfer in Pharmaceutical Industry: A review

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ABSTRACT

The term technology transfer refers to the process of movement of technology from one unit to another. The transfer may be said to be successful if the receiving unit and the transferee can effectively utilize the technology for business gain. The transfer involves cost and expenditure that should be agreed by the transferee and transferor. The success of any particular technology transfer depends upon process understanding or the ability to predict accurately the future performance of a process. This review is an attempt to understand the entire aspect associated with technology transfer.

1. Introduction

Technology Transfer, also called Transfer of Technology (TOT), is the process of transferring skills, knowledge, technologies, methods of manufacturing, samples of manufacturing and facilities among industries, governments or universities to ensure that scientific and technological developments are accessible to a wider range of users who can then further develop and exploit the technology into new products, processes, applications, materials or services. It is closely related to (and may arguably be considered a subset of) knowledge transfer. Horizontal Transfer is the movement of technologies from one area to another**[1]**.

1.1 Importance of technology transfer

Technology transfer is an important in extended benefits of R&D to the society especially in developing countries. In pharmaceutical industry preparation of dosage form needs scale up at several stages, such as small scale laboratory development from 0.5 – 2 kg batch can be scaled up to 5/10kgs and then to 20/100kg on a pilot scale. Production scale can typically range from 200kg 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. Research is carried out in laboratories on an experimental scale (small batches) before it could be producedfor commercial use (large batches). Technology transfer is important for such research to materialize on a larger scale for commercialization especially in the case of developing product. Technology transfer includes not only the patentable aspect of production but also includes the business of processes, such as knowledge and skills. Technology transfer provides an opportunity to reduce cost on drug discovery and development thus major pharmaceutical companies look for technology transfer opportunities as it reduces the risk, cost and rate of failure. The technology transfer can be happen any ways like government labs to private sectors, between private sectors of the same country, from academic to private sectors, between academy, government and private sectors of different country.

1.2 Reasons for technology transfer

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.

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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**[2-4].**

1.3 Technology transfer policy

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)**[5]** 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 fixed in this article 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,**[6]** & Good Manufacturing Practices, GMP,**[7]** 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 mergering 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**[8]**.

Although an a priori prevision results difficult, the outsourcing degree will be rather high in the area of development due to the particularities of this activity.

In order to realize one of these kinds of outsourcing, the companies observe the organizations that carry out potentially interesting research activities. In this sense, the development centers are expected to realize the activities on the same quality level and complying with the GLP and GMP guidelines, which is of fundamental importance for assuring an optimal level of operating and a strict quality assurance of the tasks established. The concept of technological surveillance proves to be an important strategic activity in the development policy of innovative companies. For this reason it seems convenient to point out the following aspects to take into account at the moment of outsourcing development functions to one of those purveyors.

- Experience in the business sector. It has to demonstrate a reputable experience
- Cultural compatibility. It should belong to the same geographic region
- Confidentiality. It should be guaranteed by signing a secret agreement
- Relations with other institutions subcontracted in turn. Application of the same rules as in the main contract.
- Financial solvency. Accreditation by a company specialized in this kind of audits.
- Technical qualification. Follow-up of a quality plan concerning facilities, equipments, staff and procedures. So a technology transfer policy in drug development can be realized as well in any direction development unit – production facility as well with new products, licensed ones or even already existing ones, concerning either the whole procedure or a part of it as it is shown in Figure 1.

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.

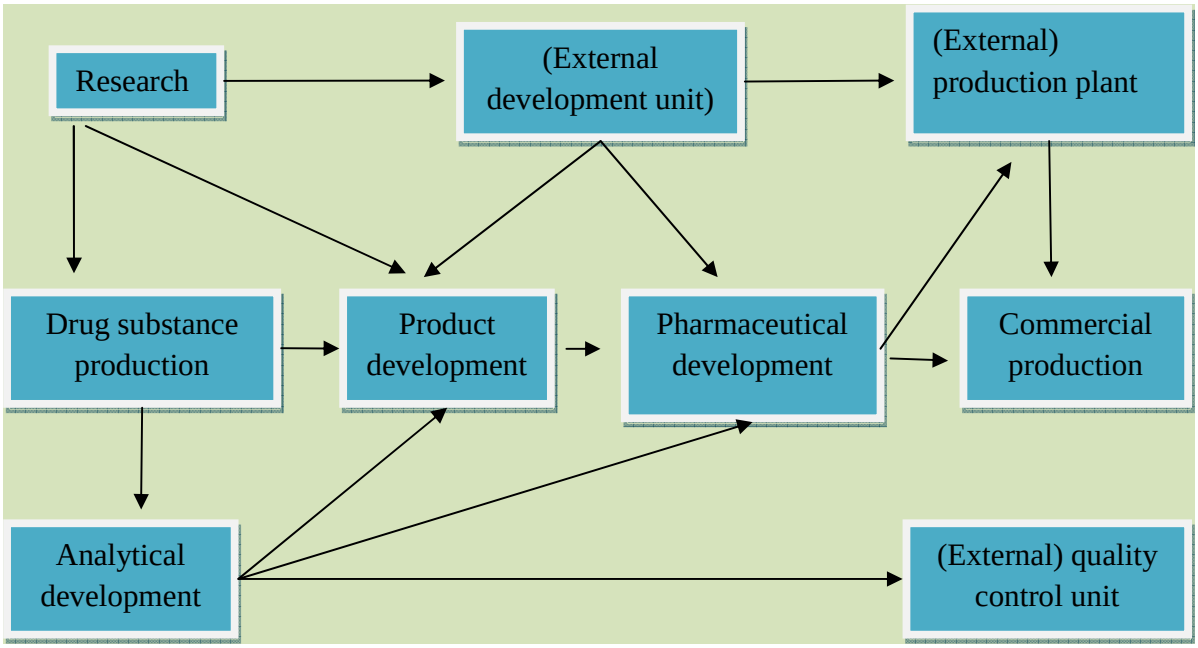

Figure 1: Technology transfer policy

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 Steps in technology transfer

The quality of design will be almost completed in phase II clinical study. Various standards for manufacturing and test will be established in process of reviewing factory production and phase III study to realize the quality of design, if design will be verified in various validation studies will be upgraded to be the quality of product and the actual production will be started. Technology transfer consists to action taken in these flows of development to realize through the quality as designed during the manufacture. Even if the production starts, the technology transfer will take place in process such as changes in manufacturing places. The processes are classified into the three categories**:**

(i). Research Phase

(ii). Development Phase

(iii). Production Phase

(i). Research Phase

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.

Drug products quality design corresponds to pharmaceuticals design-to-design properties and functions such as elimination of adverse reactions, improvement of efficacy, assurance of stability during distribution & adding usefulness based on various data such as chemical and physical properties, efficacy, safety and stability obtained from preclinical studies. For drug substance quality design is used to determine starting materials their reaction paths and basic specification of the drug.

Identification of specification and quality by R&D

Quality of product should meet the specification of an innovator product for this different stability studies are carried out for innovator product and for product which is to be manufactured.

ii. 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**[8]**.

Technology transfer from R&D to production

Transfer of the technical information is necessary to realize manufacturing formula and actual production facility. Technical information to be transfer should be compiled as R&D report.

iii. **Production Phase**

Validation 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.

Scale-up

Scale up followed after getting all information from R&D. It involved the transfer of technology and the transfer of knowledge. From sifting to film coating each process had its own set of challenges. The development of robust formulation and process through the use of Design of Experiments (DoE) as well as understanding the critical v/s non-critical parameters for each operation were be major determining factors for success v/s failure on scale-up.

The following chapter focused on the same of the scale-up issues and considerations for several unit operations that may be utilized during the manufacture of solid dosage forms. Full scale commercialization includes: Active Pharmaceutical Ingredient (API), Drug product (dosage form or delivery system), analytical methods.

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.

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.

Technical information of developed products is obtained from data of a limited amount of batches. Various standards have been established from the limited data and quality evaluation method established in development phase is not always sufficient for factory production. It is highly desired to feed back and accumulate technical information obtained from repeated

production. In addition, it is important to appropriately modify various standards established before based on this information. Accountability and responsibility for design and manufacturing should be executed.

1.5 Technology transfer documentation

Technology transfer documentation is generally considered as document indicating content 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 the duty of quality assurance department to check and approve the documentation for all processes of technology transfer.

1.6 Development report

The ultimate goal for successful technology transfer is to have documented evidences. The development report contains data of pharmaceutical development of new drug substances and drug product at stages from early development phase o finale application of approval, information of raw materials and components, rational for dosage form and formula designs and design of manufacturing methods, change in histories of important processes and control parameters, stability profile, specification and test methods of drug substances, intermediates, drug products, raw materials, which also includes validity of specification range of important tests such as contents impurities and dissolution, rational for selection of test methods, reagents and columns, and traceability of raw data of those information. This report contained the method of development as well as process development. Process development and commercial production were on critical path because of compressed time-to market expectations.

i. **Packaging development report**

This information provided details about packaging development to the concerned technology transfer person for executing the function.

ii. **Technology transfer plan**

The technology transfer plan is to describe items and content of technology to be transferred and detailed procedure of individual transfer and transfer schedule, and to establish judgement criteria for the completion of the transfer. The transferring party should prepare the plan before the implementation of the transfer and reach an agreement on its contents with the transferred party**[9, 10].**

2. Conclusion

In pharmaceutical industry, technology transfer means action to transfer of information and technologies necessary to realize quality of design of drugs during manufacturing. The three primary considerations to be addressed during an effective technology transfer are the plan, the persons involved, and the process. A plan must be devised to organize the personnel and the process steps. Once prepared, the plan must be communicated to the involved parties in research, at the corporate level and at the production site. The technology transfer does not mean one-time actions taken by the transferring party toward the transferred party, but means continuous information exchange between both the parties to maintain the product manufacturing1,5. To assure the drug quality, it is desire to make sure that is what, when, and why information should be transferred to where and by whom and how to transfer, then share knowledge and information of the technology transfer each other between stake holders related to drug manufacturing.

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