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PHARMACEUTICAL TECHNOLOGY TRANSFER: AN OVERVIEW

Md. Shoaib Alam*[1] and Javed Ahmad [2]

PDL – Formulation; Ranbaxy Laboratories Limited [1], Paonta Sahib-173025, Himachal Pradesh, India
Department of Pharmaceutics, Faculty of Pharmacy, Jamia Hamdard (Hamdard University) [2], New Delhi - 110062, India

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Correspondence to Author:

Md. Shoaib Alam

Research Scientist, PDL-Formulation; Ranbaxy Laboratories Limited, Paonta Sahib-173025, Himachal Pradesh, India

E-mail: shoaib.Alam@ranbaxy.com

ABSTRACT: The article attempts to discuss the issues associated with technology transfer in the pharmaceutical industry. A major decision focuses on that point where the idea or process is advanced from a research- oriented program to target toward commercialization. The success of any program is highly dependent on the effectiveness of the communication preceding its implementation. The ultimate goal for successful technology transfer is to have documented evidence that the manufacturing processes for drug substances and drug product, respectively, are robust and effective in producing the drug substances and drug product complying with the registered specifications and Good Manufacturing Practice requirements. The Pharmaceutical Technology Transfer activities are to transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realisation. This knowledge forms the basis for the manufacturing process, control strategy, process validation approach and ongoing continual improvement. 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.

INTRODUCTION: The technology transfer throughout the life cycle as well as transfers of manufacturing processes from one site to another during the commercial production phase [1].

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 [2].

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This knowledge forms the basis for the manufacturing process, control strategy, process validation approach and ongoing continual improvement [3]. 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 review articles is also intended to propose some regulations to realize technology transfer necessary for high quality and stable manufacturing of developed products and existing products by reviewing technology transfer based on the following ideas.

- The technology transfer means actions to transfer information and technologies necessary to realize quality of design of drugs during manufacturing.

- Appropriate technology transfer is important to upgrade the quality of design to be the quality of product, and ensure stable and high quality of the product.

- It should be noted that drugs may influence human lives and health, and their raw materials, compositions and manufacturing methods are changed during their long term manufacturing and marketing.

- To assure the drug quality, it is desired to make, 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 drug product between transferring and transferred parties.

- The technology transfer does not mean one time actions taken by the transferring party toward the transferred party, but means continuous information exchange between the both parties to maintain the product manufacturing.

Definition of Technology Transfer: Technology transfer usually involves some source of technology that possess specialized technical skills, which transfers the technology to a target group that do not possess those specialized technical skills, and who therefore cannot create the tool themselves [4, 5]. Technology transfer often involves the licensing of intellectual property rights and extending property rights and technical expertise to developing firms. In the pharmaceutical industry, "technology transfer" refers to the processes of successful progress from drug discovery to product development, clinical trials and ultimately full-scale commercialization [6]. It is the process by which an original innovator of technology makes its technology available to commercial partner that will exploit the technology [7].

Basic Policies on the Establishment of the Guideline for the Technology Transfer

- Assurance of consistency through development and manufacturing.
- Embodiment of Quality by Specifications.
- Documentation Management and Update of Technical Information.

Technology Transfer Process: The drug quality is designed based on basic data concerning efficacy and safety obtained from various studies in preclinical phases and data concerning efficacy, safety and stability of drug products obtained from clinical studies. The quality of design will be almost completed in Phase II clinical study. Various standards for manufacturing and tests will be established in process of reviewing factory production and Phase III study to realize the quality of design, and the quality of design will be verified in various validation studies, and will be upgraded to be the quality of product, and the actual production will be started. The technology transfer consists of actions taken in these flows of development to realize the quality as designed during the manufacture. Even if the production starts, the technology transfer will take place in processes such as changes in manufacturing places. The processes are classified broadly into the following five categories.

1. **Quality Design (Research Phase):** The quality design is to design properties and functions of drugs, and often performed in phases from late preclinical studies to Phase II study. For drug products, the quality design corresponds to so-called pharmaceutical design to design properties and functions such as elimination of adverse reactions, improvement of efficacy, assurance of stability during distribution, and adding usefulness based on various data such as chemical and physical properties, efficacy, safety and stability obtained from preclinical studies [8]. For drug substances, the quality design is to determine starting materials and their reaction paths, and basic specifications of the drug substances.

2. **Scale-up and Detection of Quality Variability Factors (Development Phase)**:

   a. **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 drugs designed on the basis of results from small-scale experiments. In general, this process is called the research for factory production where the quality of design will be upgraded to be the quality of product.

b. **Consistency between Quality and Specification**: When the 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 product specification that the quality predetermined in the quality design is assured as the manufacturing quality, and the product satisfies the quality of design. Manufacturing methods are established with limited amount of lots and limited resources of raw materials, the product specification should be established based on data from study results with limited lots; however, relations between upper and lower limits of manufacturing formula (compositions and manufacturing methods) and upper and lower of control limits of the product specification should be fully understood, and the consistency between the product quality and specification should be maintained.

   Also, since initial manufacturing formula and specification are established based on limited information, the consistency between the quality and specification should be fully verified after the start of manufacturing, and the consistency should be revised through appropriate change controls, if necessary.

c. **Assurance of consistency through development and manufacturing:** To make developed product have indications as predetermined in clinical phases, the quality of design should be reproducible as the quality of product (assurance of consistency). For this purpose, the 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.

3. **Technology Transfer from R&D to Production:** Transfer of technical information is necessary to realize manufacturing formula established in the above in the actual production facility. When transfer technology of new products from research and development department to production department, technical information to be transferred should be complied as research and development report (development report and recommend using the development report as a part of technology transfer documentations).

4. **Validation and Production (Production Phase):** Production is implemented after various validation studies verify that it is able to stably produce based on transferred manufacturing formula. While the manufacturing facility accepting technology is responsible for validation, the research and development department transferring technology should take responsibility for validations such as performance qualification (PQ), cleaning validation, and process validation (PV) unique to subject drugs. For validations such as installation qualification (IQ) and operational qualification (OQ), which are not unique to the subject drugs, it is possible to effectively use data of already implemented validations.

5. **Feedback of Information Generated from Production Phase and Technology Transfer of Marketed Products:** As a result of technology transfer, products are manufactured and brought to the hands of consumers. Since the technical information of developed products are 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 feedback and accumulate technical information obtained from repeated production, if necessary.

   Also, it is important to appropriately modify various standards established before on the basis of these information, and accountability (responsibility for giving sufficient explanation)

and responsibility (responsibility for outcomes of actions) for design and manufacturing should be executed. For this purpose, appropriate feedback system for technical information and documentation management of technology transfer should be established. For drugs as they have long product shelf life, documentation management should be performed assuming that the technology transfer would occur several decades after the completion of development. Also since product improvements and changes of specifications and methods are often implemented, the initial technical information should be reviewed and updated at regular intervals.

For this kind of documentation management and information updating, it is desirable to establish product specification describing entire characteristics of the product in addition to the development report, which is to be revised and updated regularly. Also as in the case of technology transfer from research and development to production, responsibilities for the technology transfer should be clearly defined, documentation of technology transfer should be prepared, and the technology transfer should be implemented through adequate exchanges of technical information.

Effective Factors in Technology Transfer: Eight factors are critical in terms of creating favorable conditions for pharmaceutical technical transfers [9]:

1. A viable and accessible local market;
2. Political stability, good economic governance;
3. Clear development priorities;
4. Effective regulation;
5. Availability of skilled workers;
6. Adequate capital markets;
7. Strong intellectual property rights (IPR) and effective enforcement;
8. Quality of the relationship between industry and government, and the extent they are able to work together effectively for long periods of time.

In the technology transfer process, the entire elements of the technology triangle (**Figure 1**) are to be transferred into organizations and not impose them solely into technology's hardware parts. Thus, they should be fully cognizant of their capabilities and requirements before launching technology transfer.

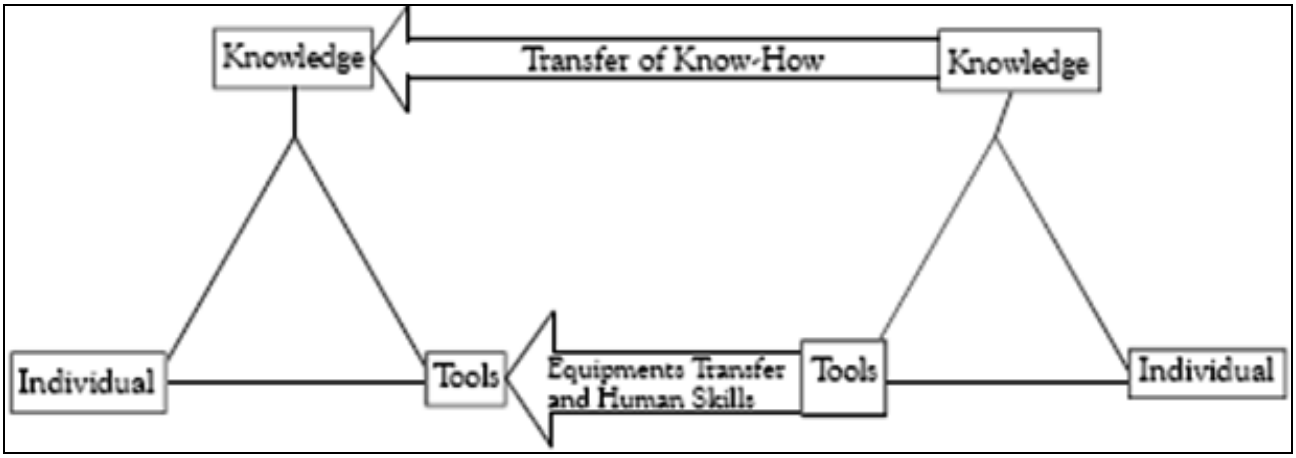

FIGURE 1: TECHNOLOGY TRANSFER PROCESS

Actually, technological evaluation, requirements and capacities recognition and selection of technology methods are of vital importance in the technology transfer process [10]. Thus, awareness of effective factors on technology transfer is of great importance for technology recipients. The paper identified and classified effective factors on technology transfer into seven main criteria each of which covers a set of sub-criteria which have been indicated in **Table 1**.

TABLE 1: EFFECTIVE FACTORS IN TECHNOLOGY TRANSFER [11, 12]

Factors and Main Criteria	Sub-Criteria
Factors relative to technology recipient organization	Long-run strategic planning in technology development; Investment in R&D; and Development of managerial and organizing skills in organizations.
Factors of Absorption and Application	Capability in absorption of importing technology; Establishing relationship between production and research; Training of individual relative to technology; and Interaction with different international centers in technology cooperation areas.
Cultural Factors	Information development in the field of technology transfer methods; Modification of cultural value systems in organizations; and Diffusion of scientific attitude in organizations.
Structural Factors	Localizing importing technology; Employment of entrepreneur managers; and Creation of standards and capabilities in companies.
Infrastructural Factors	Organizational infrastructure; Equipmental infrastructure; Informational infrastructure; and Human infrastructure.
Global Factors	Personnel training in international valid companies; Employment of international specialist in the field of technology; and Creation of appropriate relationship between recipient and sender technology.
Technological Factors	Degree of achieving technology; Degree of transferred technology price; Degree of simplicity and complicity of the technology; and Degree of development and improvement of technology on the basis of internal requirements.

The Anatomy of Technology Transfer in the Pharmaceutical Sector:

It's much more than simply handing over technology - The transfer of R&D pharmaceuticals is providing a "tool box". It occurs through many channels, all of which result in improving the economic capabilities of the recipient. Following one definition [13], we identify the following elements;

- **"Techno-ware":** for the pharmaceutical industry this would include the transfer of physical objects such as equipment for use in research laboratories or production equipment for manufacture of pharmaceuticals ingredients, or formulation or packaging of final products;

- **"Human-ware":** skills and human aspects of technology management and learning, such as a training course for researchers or general practitioners across the world Technology transfer can also create positive spillover effects into associated industries and into the supporting public sector research infrastructure;

- **"Info-ware":** all techniques related to knowledge, information and technology; in the form of a technology license;

- **"Orga-ware":** organizational and procedural knowledge needed to operate a given technology relating to a chemical or biological compound.

Strong market mechanisms provide the starting point - Foreign Direct Investment (FDI) is by far the main channel of technology transfer, but other "market mechanisms" such as licensing agreements, royalties and joint ventures are necessary channels for transferring R&D pharmaceutical technologies. Through regulation and investment, governments can help to create the right conditions for technology markets to function.

Complex map of technology transfer - The research-based pharmaceutical industry, like most other industries, is seeing the newly industrialized countries and other middle-income countries increasingly relying on technology transfer to access advanced foreign technologies and grow their domestic capabilities. The research-based pharmaceutical industry's track record is proof that in the public health arena, the historical demarcation lines such as "North-South" are being replaced by more complex networks of technology transfer. The above trend is not always shared by low income countries, and is therefore sometimes characterized by an exposure to foreign technologies and weak absorptive capacity. This creates a particular challenge for R&D pharmaceutical technology transfer and means that those parts of the world least equipped to benefit today from technology transfer are among those who need its products the most.

The Right Conditions for Pharmaceutical Technical Transfer- Commercial opportunities are paramount for the private sector when considering technology transfer, but if the basic conditions are

right, non-commercial reasons may also play a part. This is particularly true in advanced technology sectors, especially when this might provide an opportunity to open a market to a specific technology. Many countries are already well positioned in terms of R&D pharmaceutical technology transfers. Pharmaceutical and vaccine manufacturers consider a variety of factors in evaluating potential technology transfer ventures. Many of these are influenced by government policy decisions. The most effective role for governments is one of creating optimal enabling conditions, linked to the country's overall economic policy objectives.

A government's willingness to create optimal conditions to attract technology is a strong determinant of whether transfers will be directed towards their domestic industrial sector. For all investors, political stability and the rule of law are prerequisites. What research-based pharmaceutical companies are looking for in prospective recipient countries includes:

- Promising market scale and accessibility;
- Political stability and good, transparent governance;
- Appropriate capital markets;
- Innovation-friendly environment with adequate intellectual property rights and effective enforcement;
- Proper access to information;
- Adherence to high regulatory standards;
- Skilled workforce;
- Clear economic development priorities.

Stages of Technology Transfer: Typically, technology transfer occurs during one of five stages in the product's lifecycle: early discovery, toxicological evaluation, clinical development, scale-up and commercial manufacturing, and in-line production [4, 5]. Each stage involves a different type of transfer, rationale, and key participants. This transfer stages consists of good-practice guidelines and comprehensive templates that integrate the concurrent transfer work streams of drug substance, drug product, analytical methods, and packaging requirements.

The key activities for each of these work streams are aligned with good laboratory practices or current good manufacturing practices to ensure consistent and controlled manufacturing of a high-quality product. In addition, there are specific activities to address program management, documentation, and site readiness requirements. These stages help to optimize these transfer work streams and activities by:

- Addressing potential manufacturing equipment and processing constraints in the initial process design stages
- Ensuring that only the necessary transfer activities will be executed to avoid interfering with new product launches
- Managing compliance and regulatory activities
- Allocating assets more efficiently to support both ongoing production and transfer activities
- Establishing integrated plans (key activities, dependencies, inputs/outputs, and deliverables) between the sending and receiving parties.

Technology Transfer Documentation: To properly transfer technology according to the above processes, documentation of technology transfer including appropriate procedures and technical documents is necessary. Procedures and documentation of technology transfer are indicated as follows. The raw data of the documents (such as development report) should be prepared and compiled according to purposes, and should be always readily available and traceable. For successful technology transfer, task assignments and responsibilities should be clarified, and acceptance criteria for the completion of technology transfer concerning individual technology to be transferred.

In principle, it is desirable to prepare product specification with detailed information of product (drug substances or drug products) subject to transfer, then proceed with the technology transfer

according to the technology transfer plan established on the basis of this specification, and document the results as the technology transfer report. For that purpose, the following technical information should be transferred.

- The R&D department should clarify considerations of GMP compliance specific to subject drugs and manufacturing methods (manufacturing processes), and present them to a facility and equipment department.
- The facility and equipment department should establish facilities and equipments reflecting the above considerations, clearly details of the establishment and operational considerations of those facilities and equipments, and present them to a drug manufacturing department.
- The drug manufacturing department should fully understand the above information, implement validations, and perform appropriate operations and controls in conformity to the established facilities and equipments, and records results of operations and controls.

(1) Research and Development Report: The research and development report (development report) is a file of technical information necessary for drug manufacturing, which is obtained from pharmaceutical development, and the research and development department is in charge of its documentation. This report is an important file to indicate rationale for the quality design of drug substances and drug products including information such as raw materials, components, manufacturing methods, specifications and test methods. The following exemplifies information to be contained in the development report.

- Historical data of pharmaceutical development of new drug substances and drug products at stages from early development phase to final application of approval
- Raw materials and components
- Synthetic route
- Rationale for dosage form and formula designs
- Rationale for design of manufacturing methods
- Rational and change histories of important processes and control parameters
- Quality profiles of manufacturing batches (including stability data)
- Specifications and test methods of drug substances, intermediates, drug products, raw materials, and components, and their rationale (validity of specification range of important tests such as contents, impurities and dissolution, rationale for selection of test methods, regents, and columns, and traceability of raw data of those information)

(2) Product Specification (Product Specification File): The product specification is to compile information which enables the manufacture of the product, and to define specification, manufacturing and evaluation methods of the product and its quality, and the transferring party is responsible for documenting the file [14]. The product specification file should be reviewed at regular intervals, and incorporate various informations obtained after the start of production of the product, and be revised as appropriate. The product specification file should contain the following.

- Information necessary for the start and continuation of product manufacturing
- Information necessary for quality assurance of the product
- Information necessary for assurance of operation safety
- Information necessary for environmental impact assessment
- Information of costs
- Other specific information of the product

(3) Technology Transfer Plan: The technology transfer plan is to describe items and contents of technology to be transferred and detailed procedures of individual transfer and transfer schedule, and establish judgment criteria for the completion of the transfer. The transferring party should prepare the plan before the implementation of the transfer, and reach an agreement on its contents with the transferred party [15].

(4) Technology Transfer Report: The technology transfer report is to report the completion of technology transfer after data of actions taken according to the technology plan is evaluated and the data is confirmed pursuant to the predetermined judgment criteria [16]. Both transferring and transferred parties can document the technology transfer report; however, they should reach an agreement on its contents [17].

(5) Approval by Quality Assurance Department: It is desirable that the quality assurance department should establish confirmation process for all kinds of technology transfer documentation, and should check and approve the documentation.

Technology Transfer Dossier (TTD): The site/designee shall receive a Technology Transfer Dossier from R & D to another manufacturing site. The following items are part of dossier.

- Molecule information
- Proposes Markets
- Master Formula Card
- Master Packaging Card
- Storage Requirements
- Expiry
- Raw Material/Packaging and labeling Specifications proposal
- Environmental, Health and safety requirements
- Proposed Master Formula
- Detailed description of the process
- Critical parameters of the process
- Shipping requirements
- Standard test procedures for Raw materials/packing materials/in-process/Finished product specifications.
- Finished Product Specifications
- Special Sampling requirements if any
- Stability testing requirement
- Product Development Report.

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 manufacturing. 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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