EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 1
Issue: 2
Page No: 49-77
Year: 2014

TECHNOLOGY TRANSFER: A TECHNIQUE FOR PROVIDING NOVELISTIC PLATFORM TO DEVELOP QUALITY AND EFFICIENCY IN PHARMA SECTOR

Abhijeet Ojha*, Mini Ojha

DIT-University Faculty of Pharmacy Mussoorie Diversion Road Makkawala, Dehradun Uttarakhand India-248009.

Article Received on 05/08/2014 **Article Revised on 28/08/2014** **Article Accepted on 20/09/2014**

***Correspondence for Author**
Dr. Abhijeet Ojha
DIT-University Faculty of Pharmacy Mussoorie Diversion Road Makkawala, Dehradun Uttarakhand India-248009.

ABSTRACT

The article highlights various aspects associated with technology transfer in the pharma sector. Technology Transfer in Pharmaceutical Industry has been viewed from the perspective of Innovation and Research & Development The success of any particular technology transfer depends upon process understanding or the ability to predict accurately the future performance of a process. Technology transfer is a process to transfer information and technologies necessary to manufacture quality drug product consistently or technology transfer is the process of taking an invention from its inception in a laboratory to a commercialized product. The Pharmaceutical technology transfer are based on to transfer product and process related concept between initial stage of development and manufacturing stages, or between manufacturing sites to achieve product realization. This concept forms the basis for the manufacturing process, control strategy, process validation approach and ongoing continual improvement.

KEY WORDS: Pharmaceutical industry, commercialization, Research phase, Universities, manufacturing.

INTRODUCTION

Technology Transfer is defined as “the process of taking an invention from its inception in a laboratory to product development phase and then to a commercial scale. The technology

transfers are associated one side to manufacturing processes and other side with commercial production phase. 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. Technology commercialization does not happen quickly. Commercialization of radically new technologies can take well over decade.This knowledge forms the basis for the manufacturing process, control strategy, process validation approach and ongoing continual improvement.[1] 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 an original innovator of technology makes its technology available to commercial partner that will exploit the technology. Technology transfer is both integral and critical to drug discovery and development for new medicinal products. 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. 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.[2] 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. Technology transfer often involves the licensing of intellectual property rights and extending property rights and technical expertise to developing firms. 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.[3]

CLASSIFICATION OF TECHNOLOGY TRANSFER: The work of **Hayami, Ruttan (1971) and Mansfield (1975)** provide some of the earliest insights on the modes of technology transfer which are of relevance even today.

Mansfield (1975) classified technology transfer into vertical and horizontal technology transfer.

Vertical transfer refers to transfer of technology from basic research to applied research to development and then to production respectively.

Horizontal transfer refers to the movement and use of technology used in one place, organization, or context to another place, organization, or context.

Souder (1987) refers to the former as internal technology transfer and the latter as external technology transfer. Souder further elaborates upon vertical technology transfer as a managerial process of passing a technology from one phase of its life cycle to another. This elaboration is valuable because it serves to reinforce the fact that it may be possible to horizontally transfer technology at any stage of the technology life cycle.

Hayami, Ruttan (1971) and Mansfield (1975) refer to Material transfer, Design transfer, and Capacity transfer.

Material transfer refers to the transfer of a new material or product while **Design transfer** corresponds to the transfer of designs and blueprints that can facilitate the manufacturing of the material or product by the transferee.

Capacity transfer involves the transfer of know why and know-how to adapt, and modify the material or product to suit various requirements. While Hayami and Ruttan focused on **Agricultural technology transfer**, Mansfield emphasized **Manufacturing technology** [3, 4]

GOALS OF TECHNOLOGY TRANSFER [5]

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/or adjusted at scale-up

CONTENT OF TECHNOLOGY TRANSFER [6,7]

6P's of perfect technology transfer are as Proper Research – By proper research we mean firstly that in which the result are reproducible and issues such as scale up, stability etc and other practical now has been addressed, also that in which problem were taken up in first place.

Proper work- This refers to institutional and guidelines regarding IP Protection licensing modalities etc. which must be in place beforehand. In the absence of these, decision get delayed, lack of fairness in decision e.g. case of X institute, which came up with good technology but since no guidance were there, kept running around for two years and then gave up.

Pricing – most difficult and critical area of Transfer of technology. - Too high price can put off buyer, leaving the technology unsold. - Too price a result in revenue loss. - There are basically two model regarding pricing Price charged for a technology should depend upon market force i.e. impact of the technology irrespective of amount spent on developing it. Price charged should include all expenses involved in developing it.

Publicity – It is important to identify and then approach buyer i.e. adopt targeted Publicity and not blanket publicity. Specific journal, website, letters to manufacturer, personal selective visit etc. are some common approach which help in locating buyer.

Partnership – this means working along with industry. Industry takes it up, manufacturer and makes available to society. Partnerships are important to ensure your technology is successfully adopted simply conveying the details may not be sufficient.

People's Acceptance – It is no use trying to develop a technology which people will not accept e.g. due to religious reason/social concern etc. genetically modified food, irradiated vegetables processed beef in India, improved capsule made of non-vegetarian material.

IMPORTANCE OF TECHNOLOGY TRANSFER

The ultimate aim for successful technology transfer is to have documented evidence that the manufacturing process for drug substance and drug products are effective in producing the drug and drug products as per registered specifications and Good Manufacturing Practice requirement. Technology transfer is an important in extended benefits of R & D to the society especially in developing countries. Research is carried out in laboratories on an experimental scale (small batches) before it could be produced for 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 aspects of production but also includes the business 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. Technology Transfer is not a single way process. Whether it's 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.[1,2,7]

In general, Technology Transfer is the practice of transferring scientific findings from one organization to another for further development so that new products such as medicines, educational tools and health services so that they can become available to the public and by which basic science research and fundamental discoveries are developed into practical and commercially relevant applications and products. In 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 as shown in or it is the process by which a developer of technology makes its technology available to commercial partner that will exploit the technology [5,7]

REASONS FOR TECHNOLOGY TRANSFER [6,8]

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.

5. Forming alliances with partners that can progress the development of the technology to take it to market: The developer of the technology might have the resources to take the technology to particular state of development, such as up to animal studies and toxicology studies, but does not have the resources to take the technology through its clinical and regulatory phase and must collaborate with another organization to take it through these phases, and into the market.

6. Forming alliances with partners with manufacturing capability: The developer of the technology may have taken the technology to a state of development so that it is near market ready, but does have the clean room manufacturing capability or resources to manufacture the product, and must partner with another organization that does have that capability.

7. Forming alliances with partners with marketing and distribution capability: The developer of the technology may have fully developed the technology and even have obtained regulatory approvals and product registrations for the product to be sold, but it lacks the marketing and distribution channels to give it a marking capability and must collaborate with another organization that does have that capability.

8. Exploitation in a different field of application: 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 applications. By transferring the technology for the use in another field of application to

another person, the developer of the technology creates another income stream from the exploitation that takes place on that takes place in that other field.

9. No commercial capability: The developer of the technology may be research institute of a university, which does not have the capability to exploit commercially at all, and need to collaborate with another organization that does have that capability. In the exploitation of pharmaceutical products, technology transfer by collaborating with this way to bring a pharmaceutical product to market is common feature of the industry.

10. Application in different field: - With a view to create another source of income the developer may transfer the technology to another person for use in another field of application that is different from the field the technology is already applied.

11. **To launch the product commercially**:- If the developer of the technology does not have the capability to carry out the clinical and regulatory phases, he may collaborate to take it through these phases and then into the market.

12. **Lack of distribution and marketing channels**: - After fully developing the technology and getting necessary regulatory approvals to sell the product, the developer of the technology might have to collaborate with other organizations with marketing and distribution capability.

STEPS IN TECHNOLOGY TRANSFER [6,7,8]

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 as follows:

1. Development of technology by R&D. (Research Phase)

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 tests and compatibility studies are done.

b) Identification of specifications and quality by R&D: 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.

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

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

a) Master formula card (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.

b) Master packaging card: It gives information about packaging type, material used for packaging, stability profile of packaging and shelf life of packaging.

c) Master formula: It describes formulation order and manufacturing instructions. Formulation order and Manufacturing Instructions gives idea of process order, environment conditions required and manufacturing instructions for dosage form development.

d) Specifications and standard test procedure (STPs): It helps to know active ingredients and excipients profile, in- process parameters and specifications, product release specification and finished product details.

e) 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.

f) 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.

g) 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

h) 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.

3. Optimization and Production. (Production Phase)

a) 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 Validation studies verify that process is stabilize the product based on transferred manufacturing formula and Production is implemented after validation studies. Manufacturing department is accepting technology and responsible for validation.

b) Scale up for production: Scale up involves the transfer of technology during small scale development of the product and processes. It is essential to consider the production environment and system during development of process. Operators should concentrate on keeping these things in mind that their segment of the production process running smoothly if technology transfer is implemented thoughtfully. Effective technology transfer helps to provide process efficiency and maintain product quality.

4. Technology transfer documentation

Technology transfer document demonstrating the contents of technology transfer from transferring and transferred parties. Every step from research and development 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 ultimate goal for successful technology transfer is to have documented evidences. The R & D report is a file of technical 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 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. In addition, this report can be used as raw data in case of post-marketing technology transfer. The development report contains:

●Data of pharmaceutical development of new drug substances and drug products at stages from early development phase to final application of approval

●Information of raw materials and components

●Rational for dosage form & formula designs and design of manufacturing methods

●Change in histories of important processes and control parameters

●Stability profile, specifications and test methods of drug substances, intermediates, drug products, raw materials, and components, 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

●Verification of results.

c) Report: Report completion of technology transfer is to be made once data are taken accordingly to the plan and are evaluated to confirm that the predetermined judgment criteria are met. Both transferring and transferred parties can document the technology transfer report; however, they should reach an agreement on its contents.

5. Exhibit

After taking scale up batches of the product, manufacturing of exhibit batches takes place. In case of exhibit, batch sizes are increased along with equipments and their processes. This is done for filling purpose in regulatory agencies.

STAGES OF TECHNOLOGY TRANSFER [9, 10]

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. 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. The product specification file should be reviewed at regular intervals, and incorporate various information 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.

(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. Both transferring and transferred parties can document the technology transfer report; however, they should reach an agreement on its contents.

(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) [11]

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.

TECHNOLOGY TRANSFER PROCESS [9, 11]

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 categoriese.

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.

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.

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.

METHODS OF TECHNOLOGY TRANSFER [12, 13]

Technology Transfer can be done in various ways such as contract Research and Development, establishment of joint ventures, setting up plants, licensing patents, designs etc. Licensing is however the most common method of technology transfer that grants the right to use the technology in return for agreed payment. 2 main strategies of Licensing are:-

1. **LICENSING IN:** In this strategy, companies that are small and lack facilities to do basic research would wish to buy other's research. Also large scale and research based companies also might like to license in technology to expand its product line.

2. **LICENSING OUT**: In this, small scale companies that only have patents as their assets and cash in scarce would like to license out, whereas large companies license out technology if it is of very little knowledge for them.

(Ranbaxy, India's one of the leading pharmaceutical companies, is involved in both licensing in and licensing out opportunities for NDDS, Branded Generics and generics in developed and developing markets. On the other hand, Ranbaxy is looking for out licensing opportunities in therapeutic categories such as respiratory and anti infective.

TECHNOLOGY TRANSFER AGENTS [13]

1. R &D UNIT: - Universities, Public Research Centres, Technology Institutes

2. Companies: - Supplier of technology & R&D to third parties, Spin-off, start-ups, Large R&D department.

ORGNISATION OF TECHNOLOGY TRANSFER [10, 14]

Since a team concept is always the best approach to accomplishing a successful technology transfer project. The core technology transfer team should be commissions immediately following the decision of executive management to pursue the drug candidate to commercialization. Typical technology transfer core team will likely be comprised of individuals reprehensive of different segments of the business.

1. Project Manager- For overall responsibility, coordination and progress communication to management. His or her role may be enhanced as necessary by additional staff & responsibility & authority delegated as appropriate.

2. Regulatory Affairs- For coordination of the appropriate regulatory filings, advice on approval timing, content of the filing documentation & response to regulatory inquiries.

3. Engineering- To coordinate associated capital projects & direct & control construction, equipment acquisition, installation & qualification.

4. Material management- To include those units responsible for pure chasing, Strategic planning, resource allocation & supply chain activities. This member (or members) will analyze & recommend the most favorable manufacturing strategy in consideration of internal capability, business partnership & tax advantages for the corporation.

5. Manufacturing operations- To represent the originating site and receiving location production activities. These representatives should have sufficient authority to commit the necessary personal & plant resource to accomplish the project within the defined cost & time limitations.

6. Research and Development- To support the technical issues and resolve problems. This group provides the process expertise and would be expected to train and direct the production trials at receiving site.

TECHNOLOGY TRANSFER TEAM [8, 14]

The technology transfer team members and their responsibilities are as follows:

1. Process Technologist

a) Central focus for transfer activities.

b) Collates documentation from donor site

c) Performs initial assessment of transferred project for Feasibility, Compatibility with site capabilities and Establishes resource requirements.

2. Q.A Representative

a) Reviews documentation to determine compliance with marketing authorization (MA).

b) Reviews analytical methods with QC to determine capability, equipment training requirements.

c) Initiates conversion of donor site documentation into local systems or format.

d) Initiates or confirms regulatory requirements, e.g., change to manufacturing license; variations to MA if process changes needed, etc.

3. Production Representative

a) Reviews process instructions (with process technologist) to confirm capacity and capability.

b) Considers any safety implications, e.g., solvents; toxic; sanitizing materials.

c) Considers impact on local standard operating procedures (SOPs).

d) Considers training requirements of supervisors or operators.

4. Engineering Representative

a) Reviews (with production representative) equipment requirement.

b) Initiates required engineering modifications, change or part purchase.

c) Reviews preventative maintenance and calibration impact, e.g., use of more aggressive ingredients; more temperature sensitive process, and modifies accordingly.

5. QC Representative

a) Reviews analytical requirement.

b) Availability with instruments.

c) Responsible for analytical method transfer for drug substance and drug product.

MISSION OF TECHNOLOGY TRANSFER TEAM [11,15]

• The mission of technology transfer team is to develop and implement a methodology that ensures the effective and efficient transfer of robust and well documented candidate production processes from development to manufacturing.

• 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.

• Filing of the drug product in different regulatory markets or countries for approval through an effective technology transfer.

•Construction of technology roadmaps in priority areas to define future trends to avoid the pitfalls of buying out-dated, inappropriate technology and ensure non-obsolescence of technology.

• Preparation of a detailed technology transfer agreement.

• Preparation of a detailed technology transfer implementation plan based on the decisions reached during negotiations.

• Preparation of a scheme to assess the impact of a technology transfer project from market, financial, technological and organizational perspective.

FACTORS INFLUENCING TECHNOLOGY TRANSFER [5,16]

(A) Drivers for Technology Transfer

1. **Good business and manufacturing practices**: The Company's success is primarily the result of its adoption of good business and manufacturing practices, particularly in the areas of product identification and formulation technology.

2. **Potential for competitive pricing**: Balance cost to remain competitive by having higher private sector prices and very low public sector prices.

3. **Strategic planning**: Create an enabling environment for vertical integration, with prospects for higher capacity utilization and eventual lowering of production costs.

4. **Strong economy and environment**: For technology transfer to be successful there needs to be supportive business and scientific environment in the recipient country, and that environment should include skilled workers, economic and political stability, supportive regulatory environment, market size and potential and a well developed national infrastructure of natural resources and transport.

5. **Transparent and efficient regulation**: Pharmaceuticals are necessarily a high regulated industry and the regulatory function must be efficient and transparent for technology transfer to be economically viable.

6. **Opportunities for contingency supply**: Multinational pharmaceutical companies are inclined to transfer technology to local manufacturers with the potential to receive when they foresee an inability to meet time scales and volume demand from large procurers.

7. **Access to new machinery, training, know-how and business partnership**: This makes the prospect of technology transfer very desirable to local pharmaceutical manufacturers since the technology, equipment, etc. could be applied profitably beyond the initial purpose.

(B) Barriers of Technology Transfer [7,16]

1. **Lack of efficiency**: Automation of production processes to improve efficiency and lower costs.

2. **Low market share**: Local producers face significant challenges in meeting International Quality Standards and capturing a critical market share. Greater market share would increase profitability.

3. **Cost of prequalification**: There is benefit in meeting International Standards since it opens up the opportunity for trading across the entire world.

4. **Labour issues**: The pharmaceutical sector demands relatively skilled labour. High labour turnover and absenteeism owing to unattractive conditions of service is negative contributor.

APPROACHES TO OVERCOME BARRIERS IN TECHNOLOGY TRANSFER [6,17]

1. **Commercializing publicly funded technologies**: The basic pattern envisioned is to give institutions receiving public research funds the right to obtain and exploit patents on inventions developed in the course of research.

2. **Research tool patents and freedom to operate for the public sector**: Patents sometimes make it difficult for public researchers to carry out their research or to make the products of that research available. It is intensified by the tendency of some publicly funded research laboratories to avoid use of a patented technology without permission even in nations where no relevant patent is in force.

3. **Web access and scientific publication**: Limited access to scientific journals led to enormous problems for developing nations scientists.

4. **National security issues and restrictions on exports of particular technology**: International controls designed to protect national security and to prevent the proliferation of important technologies also restrict the flow of technologies.

5. **Co-operative research agreements**: Global support for public sector research might be encouraged is through co-operative research agreements designed to meet specific goals. It would seem more feasible to focus efforts on technologies of significant social benefit to the developing nations.

6. **Possible treaty on scientific access**: There has also been a proposal for an international treaty on access to knowledge and technology negotiated on the basis of the type of reciprocity found in normal international trade negotiations. The concept is mean to be non-zero sum in the sense that, like free trade in goods, free trade in scientific ideas benefits all, and such arrangements could be made bilaterally as well as multilaterally.

TECHNOLOGY TRANSFER POLICY [17,18]

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 fixed 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 and 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 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

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. 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.

EFFECTIVE FACTORS IN TECHNOLOGY TRANSFER [3,4,18]

Main factors that affect the process of technology transfer in pharmaceutical industry are as follows**:** ● A viable and accessible local market; ●. Political stability, good economic governance; ●**.** Clear development priorities; ●. Effective regulation; ●**.** Availability of skilled workers; ●**.** Adequate capital markets; ●**.** Strong intellectual property rights (IPR) and effective enforcement; ●. Quality of the relationship between industry and government, and the extent they are able to work together effectively for long periods of time. ●. Investment in Research and Development, ●. Establishing relationship between production and research, ●. Training of individual in relation of technology, ●. Information development in the field of technology transfer methods, ●. Organizational, Equipmental and Informational infrastructures, ●. Employment of International specialist in the field of technology and creation of appropriate relationship between recipient and sender technology, ●. Awareness of fundamental and important factors required for technology transfer, ●. Consideration of existing and old technologies, ●. Degree of development and improvement of technology on the basis of internal resources.

In the technology transfer process, the entire 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.

WAYS OF "TECHNOLOGY" TRANSFER [10,13,18]

There are several ways of technology transfer like:• In print through technical journals,• In print through learned journals,• Scientific magazines,• Patents• Orally at conferences,• Orally at learned societies,• In discussions with colleagues,• In discussions with acquaintances,• In discussion with consultants,• On television or radio,• Courses,• Service bulletins,• Data packs,• Specifications.

SUCCESS OF TECHNOLOGY TRANSFER [9,19]

The different **"C"** for successful technology transfer is: **Communication**, **Certainty**, **Challenges**, **Capacity** and **Commitment**

 Communication: The technology transfer chain is often long, in terms of both distance and time. Effective communication is thus another essential ingredient in the recipe for successful technology transfer. Efficient and effective two way communication and corporation between key stakeholders will do much to remove barriers.

 Certainty: A lack of certainty, and the consequential high levels of risk, both real and perceived, are recognized a major impediments to the successful establishment and ongoing operation of functional markets. Removing barriers to technology transfer often translates into increased certainty, and decreased risk, for the key stakeholders such as developers, suppliers and recipients.

 Challenges: There are many barriers to successful technology transfer. All along the transfer path, from the supply side of technology to demand side, impediments occur at very node and, due to restrictions on movement of information and materials, for every linkage in technology transfer chain.

 Capacity: Enhancing the transfer of technologies that support sustainable development in largely about creating favorable circumstances for technology transfer-ensuring all stakeholders have the ability to fulfill their roles and meet their responsibilities, expeditiously. All key players and stakeholders must have the necessary knowledge and skills to perform the roles and tasks expected of them.

 Commitment: For a successful technology transfer there may be a good commitment to overcoming the challenges, providing technology users with the choice they deserve and desire, increase certainty, reducing risks, enhancing the communication between technology transfer stakeholders and building and strengthening the enabling environment and thus the capacity for Technology transfer.

FACETS OFTECHNOLOGYTRANSFER [6,19]

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.

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.

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.

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.

KEYS AND WAYS OF SUCCESSFUL TECHNOLOGY TRANSFER [11,12,19]

The key to successful technology transfer is:

(a) Amalgamate strategy, organization and processes both within and across organizations which should be customer-focused. Customer focused strategy helps ensure configuration of regulatory requirements and filing strategies. To augment the competence of technology transfers and minimize the risk of late-stage site changes, the companies must strategically select sites to match their product's technology, process, and capacity requirements early in the development process.

(b) The next job is meticulous selection process of contract manufacture organization. Looking at the objectives one must adopt a very rigorous process in the selection and based on the requirements on business, technical, quality and regulatory aspects. The companies which are selected go for establishment of non-disclosure agreement with companies they are interested to allow for more comprehensive discussions.

(c) Establishment of timeline and cost-savings objectives for the transfer.

(d) Highly skilled, dedicated technology transfer teams with excellent managerial skills.

(e) Technology transfer takes place during one of the stages in the product's lifecycle: early discovery, toxicological evaluation, clinical development, scale-up and commercial manufacturing, and in-line production. At every stage it requires different type of transfer, rationale, and key participants .So a road map is required to translate the transfer strategy into unambiguous activities, to define the timing, sequence, and dependencies among these activities, and to identify the stakeholder responsibilities and deliverables.

(f) Inspite of having excellent strategy and road map, successful technology transfer demands that the organization to which the technology is transferred must ensure that the technology is successfully implements the technology keeping in mind all the variables.

UNSUCCESSFULL TECHNOLOGY TRANSFER PROCESS [5,20]

It may be due to following reasons:-1. Unsuccessfull or incomplete Process Validation.**2**. High rates of batch rejections, excessive labour requirements, increased cost of product etc.**3**. Incomplete Documentation.**4.** Product does not show specifications as intended.**5.** Delayed regulatory approval and/or product launch.

FEW CASES OF TECHNOLOGY TRANSFER [6,8,20]

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 mechanic cal; 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.

5. Themis laboratory has entered in technology transfer agreement with Aventis pharma Ltd for the development of fixed dose combination of glibenclamide and glimepride with metformin technology patented by Themis.

6. Laboratorio Elea also possesses licences to commercialize product made by Chiron Corporation (vaccines) and Novo Nordisk (hormone therapy) and promotion agreement with Novartis for its line of transdermal patches in hormone therapy

7. National chemical laboratory (NCL) Pune has several linkages with universities and pharmaceutical industry to ensure successful scale-up, seamless technology transfer and implementation of technology

8. Shantha Biotechniques had entered in to technology transfer agreement for Typhoid vaccines with IVI, Korea.

9. Cipla has technology transfer agreement with companies in Uganda, Nigeria, Egypt, Moroco and Algeria.

ORGANISATION INVOLVED IN TECHNOLOGY TRANSFER [12,20]

World Intellectual Property Organization, National Institutes of Health Technology, Transfer Desk Reference, Biotechnology Industry Organization.

LIST OF INSTITUTES IN INDIA ASSISTING IN TECHNOLOGY TRANSFER [13,20]

1.Asia Pacific Centre for Transfer of Technology, **2**. National Research & Development Corporation, **3**. Technology Bureau for Small Enterprises, **4**. Foundation for Innovation & technology transfer.

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. 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. 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 agreed with a sending unit and/or a development unit. Appropriate efficiency in technology transfer from development to commercialization can be achieved through better communication and documentation by technology transfer team. A cooperative effort by team results in more successful initial and consistency runs leading to an earlier license, earlier launch and a greater market share.

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