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IMPORTANCE OF QUALITY ASSURANCE IN EFFECTIVE IMPROVEMENT OF TECHNOLOGY TRANSFER

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ABSTRACT

The word technology can be defined as "specialized information which is applies to complete a practical purpose". In other way,product can be developed by applying scientific information or service in order to content a current.It is also known as transfer of technology, for understanding any process it depends on the specific knowledge. The main objective of this article is to know about how Quality assurance has been used in technology transfer.Technology exists in a three main key areas; they are of knowledge, skill, and instrument. Though, the importance of techn transfer in theimprovement perspective is nothing different.The plan of project is being designed according to the quality aspects and it directly depends on quality risk management principles. How the failure of technology will leads to deviation is mentioned with one case study.

INTRODUCTION

The technology and management recognized consideration as important strategic by organizations. The Technology which has been used by organizations should allow them to be economical in the global market. The aspects surrounding technology properly and technology is managed by the organisation. Transfer of the most appropriate technology to the organization is considered as important aspect that in management. The transferring of technology from a originator environment to a handler environment.[1] Information of the technologies has been used by an organization, the technologies which exist to organizations in addition the technologies are also used by their competitors, most appropriate technology is selected by the assist decision makers. Technology exists in a three main key areas; they are of knowledge, skill, and instrument. Though, the importance of techn transfer in the improvement perspective is nothing different. More than 30 years ago, one research person recognised that, fundamental process which Effects on the economic performance of nation and firm in tech transfer. [2]

Importance of technology transfer: To evaluate all the necessary info to transferring technology from research and development for actual manufacturing process by analysing various info obtained in the research and development phase.[3] To evaluate all the necessary info for transferring technology of one drug product between different manufacturing places. To analyse the required info for technology transfer from Research and Development to a real manufacturing by organization the different information got during the R&D and the technology transfer for existing drug product between different manufacturing places. For particular working procedure and for point for the 2 types of tech transfer in the above for contributing for the tech transfer and it is applied through research and development and drug substance and drug product which is of chemically synthesized

produced and for any post marketing change in the manufacturing place technology transfer is related. To analyse the difficulties involved in transferring technology from laboratory to production phase. [4]

Requirements of technology transfer: The plan of project is being designed according to the quality aspects and it directly depends on quality risk management principles. The responsibility and potentiality of the Sending Unit and the Receiving Unit must be equal and need not to be similar but the facilities and equipment should be operated under same SOP (Standard operating Procedures). Analysis of technical gap between the SU and RU i.e., potential regulatory gaps, risk assessment should be performed and rectified as and when required. Professionally trained staff with sound knowledge should be available to provide training at the RU, management of regulatory requirements between SU and RU and verification of the same with the other countries were the product is to be exported, and this must be monitored throughout the project. This makes the effective transfer of project procedures. Projects of technology transfer, mostly those in between the companies, economic and legal implication. These issues, which include some of the intellectual property rights, confidentiality and the interest in conflict, on open communication of technical matters are expected to impact in any way; they should be addressed execution of the transfer, during planning and should be addressed before. Unsuccessful transfer of technology may be because of lack of transparency.[5]

Technology Transfer Process: The quality of the drug is designed based upon the preclinical phases and concerning data efficacy, safety and stability of drug andin Phase II clinical study the quality of design is almost completed. Different standards for developing and tests is established in Phase III study and starting the actual production. It includes the actions taken in these flows of development to know the quality, as designed in the manufacturing process. The technology transfer takes place in process if such change in the manufacturing place even after the production starts. To confirm the product specification that the quality design is assured as the manufacturing quality, and quality of design should satisfies product.[6]

Technology transfer in Sending and Receiving site:

The main step in the techn transfer is between SU and RU in pharmaceutical industry for the production of the specific product. Research and development plan is made yearly but product to be produced is specified by the management team.Later on, sending unit, formulation services from receiving site coordinate the dates for the products defined in the plan, together with the project manager at each site, who decide when each step per product has to be completed. For the formulation selection it is essential to analyses the dossier of each manufacturer, a technical package should be requested with information about the stability data, specifications, justification of specifications, analytical procedures, impurities profile, origin of each impurity, certificate of analysis and a quality commitment if required. For choosing the manufacturer it is important to make sure that the drug product is being produced with consistent quality and in a GMP facility. A material sample from the supplier should be requested to evaluate the Drug product quality, stability and degradation profile. In case it is different in any way, a handling SOP modification is required. The impurities have to be evaluated so it is important that they are available for analytical activities. However, the Drug product manufacturer should provide a statement for residual solvents, genotoxic impurities and elemental impurities. After selecting the drug product supplier, previously which has been audited by sending compliance group, it is necessary to send to receiving site, the most recent Dossier/technical package of the formulation and the Certificate of Analysis which is in compliance with the US guidelines. The price of the Drug product has to be mentioned for R&D purposes. The necessary quantities for development have to be ordered, and later on for stability/submission batches.[7]

Main Reasons for technology transfer:

1) Manufacturing volumes: The equipment's used only for small scale operation is with developer while they need to team up with

other agency to perform large scale manufacturing.[8]

2) Resources for launching product: Toxicology & animal based studies are done in pre stageand only resources need to be conducted by innovator where as they are not having sufficient resources for clinical and regulatory phases.

3) Distribution and marketing capacity: The fully developed technology is given by the technology developer and they even have product registration and they have obtained regulatory approvals, but they don't have product distribution channels and marketing ability.

4) Manipulation in various units: Every developer will have only half of the solution i.e. in the field of diagnostic applications the developer who is developing technology may of capable of exploiting technology and for the exploitation of therapeutics application exploitation right is given to commercial partner.[9]

There are 3 different phases in Technology transfer:

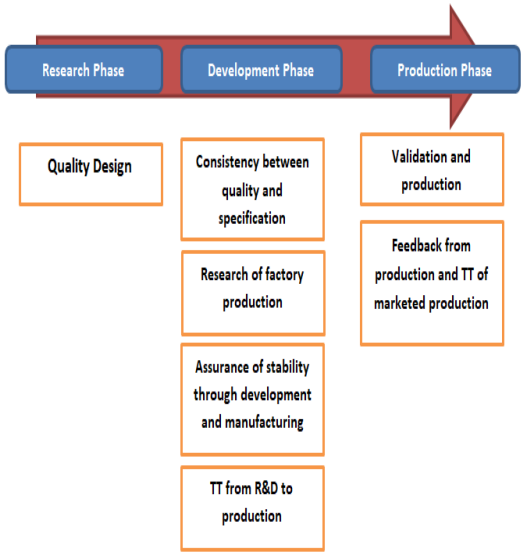
- Research phase
- Development phase
- Production phase

Research phase: The research site is responsible for the correct pharmaceutical design of the drug. This phase includes the study of the components/product efficacy, guarantee the avoidance of adverse reactions, assure the drug stability and analyses the data available to achieve a better knowledge about the product.[10]

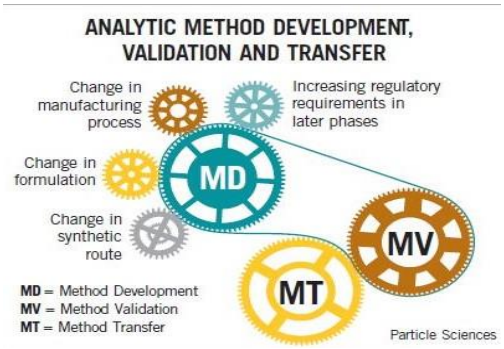
Development phase: For the manufacturing of drug product with that of designed quality, establish an appropriate is required for manufacturing process at a small scale and detect variability factors to assure that the scale-up for submission and validation purposes will be performed without difficulties. The upper and lower limits of the manufacturing process including structure and parameters should be challenged during development.[11]

Production phase: To assure the consistency between development and manufacturing, the sending person in development of the charge should be understand completelythat which type of the technical information is required receiving person of manufacturing in charge. A suitable method is required to analyse whether the drug which is manufactured is meeting the quality of design that should be executed. In case the product is similar to others before produced, it is fundamental to study the information about the process maintained by the manufacturer.[12]

Quality Control: Analytical method transfer: For any pharmaceutical development program validation, transfer, and method development are some of the key element. For the effective method improvement ensures that lab sources are optimized, some of the method meet required objective at the each stage of development of drug product. The regulatory agencies require method validation in some stages of the approval of drug; it is defined as the demonstrating that analytical producers are suitable for theintended use. It is the formal process of assessing in another laboratory with the suitable method. In the each stage continuous improvement in the method and results which are obtained is more efficient in development of drug.[13]



To make finished product have indications as fixed in clinical phases, there should be reproducible quality of design. For this reason the transferring person should



Assurance of consistency through development and manufacturing: [14][15]

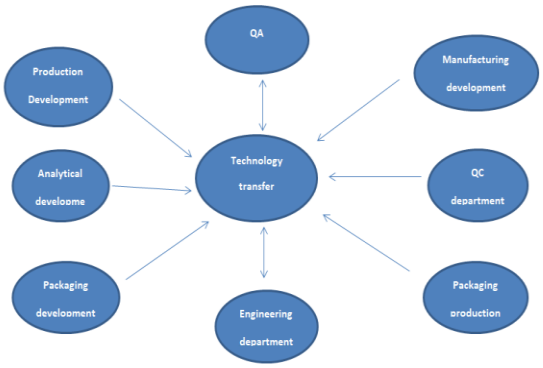
- ✓ Should provide all the required technical information by the transferred person.
- ✓ There should be a suitable evaluation method for identify, whether the drug is meeting the quality of design.
- ✓ Understand that the technical information of product are produced from data of the specific batches,
- ✓ Understand that quality method established in different phase is not sufficient for production in the factory.
- ✓ Fully refer to information of same finished products of the past maintained by the manufacturer.

Technology transfer involved in the specific department:

For new medicinal products processing in drug discovery and development technology transfer is critical and integral both. For transfer products to manufacturing sites is continuously driven by economics. The main stages of the process is collection of data, review of obtained data, and regulatory impact with that of specific emphasis on any modified approvals, full-scale batch processing , stability set down.[16]

Quality Assurance:

- ✓ To review and approve technology transfer protocol
- ✓ To review, conclude and approve technology transfer report
- ✓ To review and approve analytical method transfer protocol To review and approve analytical method transfer report



Responsibilities of technology transfer:[17]

- ✓ To provide all relevant documents to technology transfer team for effective execution of technology transfer activity
- ✓ To provide technical support during transfer of analytical methods and manufacturing process
- ✓ To monitor of critical deviations during execution of the protocol.
- ✓ To compile, review and approve Technology Transfer report
- ✓ To prepare/ ensure availability of all relevant documents at receiving unit

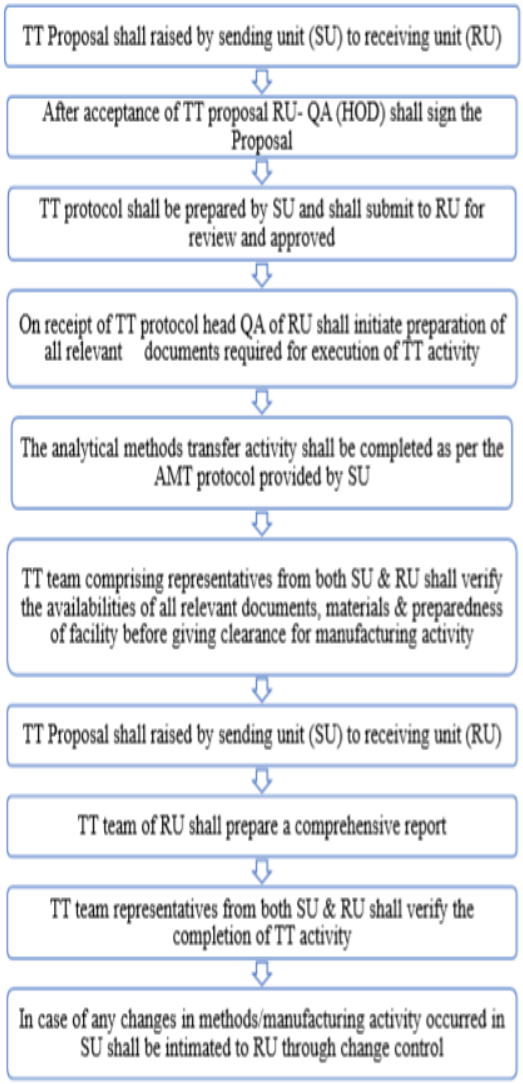
Quality Control: Transfer of analytical methods to receiving unit. Review of the protocol and report.

Production: Supporting the receiving unit in execution of the protocol / manufacturing packing activities. Review of the protocol and report.

Technology transfer procedure:

On acceptance of technology transfer proposal, evaluation of facility/ equipment and batch size suitability at receiving unit shall be performed jointly by both SU and RU.A protocol for technology transfer shall be prepared by sending unit and shall submit to the receiving unit for review and approval.On receipt of technology transfer protocol QA head /Designee of receiving unit shall verify the availability of documents as per the "Technology Transfer Checklist". QA head /Designee of receiving unit shall form a technology transfer team comprising members of both SU and RU and initiate preparation of all relevant documents required for execution of technology transfer activity, in line with the documents provided by sending unit along with TT Protocol. The analytical method

transfer shall be completed as per the protocol of analytical method transfer provided by the sending unit / relevant analytical laboratories. The method transfer for API is performed in coordination with the API manufacturer/ supplier. Ensure the Analytical method transfer is completed for all the test parameters before execution of the manufacturing activity at receiving unit. Details of API/ Excipients reference standards working standards and samples of active ingredients and finished products etc. used during the AMT at receiving unit shall be recorded. A Technology transfer team comprising representatives from both sending unit and receiving unit shall verify the availability of all relevant documents, materials and preparedness of facility before giving clearance for manufacturing activity.[18]



Documentation in technology transfer:[19][20] Steps step from product development and research should be recorded, the given and tasks that should be simplified and some of the specification should be within the acceptance limit for completing the techn transfer regarding specific technology transferred. That is the main responsibility of QA department to inspect and approving the document for all type of the process for technology transfer.

1) **Developing reports:**
   The research and development record is one of the important file in the technology transfer and the main incharge of this document is research and development. This report is an important document which gives information about quality design of drug substance, sampling method and its specification. This data is not required for submission for the approval and it is used for pre-approval for inspecting as more valid record in the quality of new drug substance.
   Developed report should contain:

   - ✓ Reports of new pharmaceutical drug product and new drug substance in the early stage development.
   - ✓ Information regarding the raw material used and component.
   - ✓ Quality design for manufacturing.
   - ✓ Changing of histories of some important parameter and processes.
   - ✓ Drug substance sampling method and its specification.
   - ✓ Verification of output results.

2) **Technology transfer plan:**
   It is to give information about the materials of the technology that is to be transferred with a detailed method of transfer schedule and the individual transfer . Before implementation of the of the plan the transferring party should be prepared for transfer and agreement is signed pn its content with the party.
3) **Technology transfer report:** After completing of the tech transfer all the data should be recorded and that is accordingly plan of technology that is calculated to confirm criteriafor the

judgement are to be meet. Report of technology transfer should be recorded by both transferring party and also by transferred parties.

Organization of technology transfer:[21]

The concept for effective technology transfer is team concept. The technology team should start their work immediately getting order from the management for the purpose of the drug candidate commercialization. There are different types of segment in the business.

1) **Project manager:** His role is to increase all the necessary addition staff requirement and responsibility. He is the person who is responsible for communication all the information regarding technology transfer.
2) **Regulatory Affaris:** In this coordination of the content of filing document , regulatory filing, response to regulatory and advice on approval timings.
3) **Engineering:** Installation and qualification, equipment management, control construction,
4) **Material management:** For internal capability and tax advantage most favourable manufacturing strategy is considered. For including those type units for the responsible of planning strategy, supply chain activities, allocation of resource.
5) **Manufacturing operation:** It represents the production activity of the receiving location and originating unit. This originating site and receiving location should have adequate power for committing all the required resource for both personal and plant for completing the work should be within the certain limitation and predefined price.
6) **Research and Development:** This required for the solving the problems and any technical issues. This provide process expertise and for training and directing the production at the receiving site.

Factors influencing technology transfer:

Drivers: [22][23]

The countries have a supportive environment that includes strong intellectual property and enforcement for successfully to attract imported technology, which facilitates the transfer. Factors as skilled workforce working together such as engineers and managers also contribute to efficiency in the results. Increased information exchange including effective systems that identify who is interested in purchasing the technology and entities ready to transfer their technology are easy ways to facilitate the task. The probability of technology transfer can be very advantageous to local pharmaceutical maker or producer even in another viewpoint. The technology, new machinery, training, among other transfer additional benefits can then be applied profitably for other production purposes.

Barriers:[24]

The lack of government focus at times towards the technology transfer approach and the high cost for prequalification can also bring complications, monetarily. The funding on important areas of research should also be higher. Furthermore, there are controls and restrictions on technology exportation established by national security which makes it harder to perform the transfer internationally. Another problem found is the reduced access to online scientific journals, for theR&D site it can raise difficulties during the development process.

Advantages of technology transfer:**[25]**

- ✓ The more effectively knowledge is shared within and organisation.
- ✓ Cost effective production and distribution.
- ✓ Innovative Research and development, drug approval, effective commercialization, ensure safe, effectiveness in drug product.
- ✓ With new technology people can do work in an effective way.
- ✓ Well defined products can be developed with transfer strategy.
- ✓ Through administrative sponsorship of the project proactive decision can be made.

- ✓ Measure for standard performance for the team work and processes.
- ✓ High quality performance and cross functional team.
- ✓ Leading edge process in management tool and document.
- ✓ On the basis of the preclinical phase the drug quality can be designed.
- ✓ Adverse reaction can be easily eliminated.
- ✓ Effectiveness of the drug can be improved.
- ✓ It provides technical information about the transferring party.
- ✓ It gives information about organization complies with the Good manufacturing practice.
- ✓ It gives complete over view information about the manufacturing methods.

Case study:

Introduction:

Computer aided software is considered as important tool in different industries to speed up process and decrease costs. However this software product contains various defects which will go undetected for a long period of time**[26]**. Overtime time they may appear suddenly. In this case study, we have explored the software quality assurance in the case of **Therac-25** and discussed about how improper use of software results in incidents. To develop high quality software with an acceptable quality in the health care sector is an integrated role of an engineer and a pharmacist.[27]

Introduction of Therac-25:

The linear medical accelerator called Therac-25 is used to cure patients having different types of cancer in various parts of their bodies. This deviser is the successor of two previous devices (Therac-6 and Therac-20) having few common features with these two devices. Therac-25 was manufactured by AECL solely. It works in two modes of beams by the contrast of its predecessor and Therac-25 first mode was electron beam which was mostly used for surface treatment of cancer and the other mode is X-ray mode (photon mode) which worked with a pre-set 25 MeV (Million electron Volt) for treating cancer tumors located in depth with make the lowest possible destruction to the other parts by placing the metal foil in the path of the beam. Therac-20 and 25 both could produce the electron and photon beams. [28]

Review on incident: Therac-25 was involved in some major accident in the years between 1985-1987 until this device was discontinued and recalled to changes in its software and hardware. In all the failure observed patient has been received more quantity dose than that of prescribed resulting in radiation overexposure or radiation burns ultimately costing the life of that person.[29]

The Scenario: Out of the six accidents occurred the first was on June 3, 1985 when a 61-year old patient was treated by Therac-25 in Kennestone Regional Oncology Center (Marietta, GA) for the removal of a malignant breast tumor. She was in the treatment process and was familiar about the treatment and its procedures but at the accident time Patient described, she felt a “tremendous force of heat a red-hot sensation.” On that time she had complained to the operator regarding the matter but no action had been taken by the operator and hospital as there was no sign of the radiation detected. Two weeks later after the accident, the physicist noticed that Patient had a matching burn on her back, as a sign of the burn had gone through her body. The swelling on her back had also begun to slough off the skin. Patient was in great pain, and her shoulder had become immobile. These clues led the physicist to conclude that patient had indeed suffered a major radiation burn. It had been estimated that patient had received around 20,000 rad (radiation absorbed dose) which was 100 more than prescribed dosage (200 rad). After the accident the physicist called to AECL and without informing them regarding the accident asked questions about the possibility of overexposure in Therac-25. Three days later AECL engineer called to the physicist and mentioned that there is no chance of overdosing. As a result, the hospital was not able to identify the cause of overexposure and the case just was ignored, finally the patient lost the use of her left shoulder; arm and her left breast had been removed due to the radiation burns or radiation over exposure.[30]

Identification of failures:

1. **Lack of proper inspection:** Dearth in proper periodic inspection on designed software can lead to accidents. The inspector who is going to inspect the software should look at software code properly with detailed code reviewing. Based on what is mentioned it can be concluded that for the critical software the inspection method was not proper or not and efficacy of efforts made can also be analysed.[31]
2. **Lack of testing:** Any shortage in the quality of testing of the software can also contribute to errors.[32]
3. **Lack of training:** Giving proper training for the operator can eliminate all the possible deviations. The operator should be educated, such that he has some basic knowledge about software.
4. **Mall function error confusion:** Error messages displayed on the Therac-25 were confusing and this was not properly understood and communicated to the operator.[33]

Proper training regarding the error massage understanding will leads to less deviation.

Quality to detect software defects:[34]

- Quality assurance in the planning phase
- Quality assurance in implementing phase
- Quality assurance in the testing phase
- Quality Assurance in the maintenance phase

Conclusion for case study:

Thus, Therac-25 was one of the medical devices of mid to late 1980's, with caused some accidents because of software failure. In this case study analysis we reviewed how to improve the quality assurance aspects in any software or a technology transfer. A proper quality assurance could have prevent the incidents caused by Therac-25. We here by conclude that SQA (Software Quality Assurance) is a mandatory aspect to be concentrated on to assure an error free transfer of knowledge in short for a proper utilization of the software technology for a better health care delivery.

CONCLUSION:

To improve the quality of design of any product suitable technology transfer is require. By doing proper communication in between the different units and some organisation success rate of technology transfer can be increased. All required info should be provided for effective technology transfer. It involved in the transferring of the info and required technologies for improving the quality of the drug product. Suitable plans are prepared and these plans must transferto involved parties who are involved in research. For better understanding about failure of technology transfer one case study is included in this article.

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