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Guidelines for a pharmaceutical technology transfer towards a drug manufacturing plant

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Abstract. The establishment, every time more needed, of a technology transfer program in the area of drug development with regard to its future production is a complex process that involves two sides, the knowledge donor and the manufacturer of the finished drug as its acceptor and, particularly, some complex and huge pharmaceutical units as a typical pharmaceutical structure. Both sides' mutual, sincere and convinced acceptance of a series of guidelines described with respect to drug development, manufacturing, specifications, analytical development and regulatory affairs must meet the above mentioned aims

Key words: Pharmaceutical technology, technology transfer, guidelines

Resumen. El establecimiento, cada vez más necesario, de un programa de transferencia de tecnología en el campo del desarrollo de un medicamento para su posterior fabricación es un proceso complejo que implica dos partes, el donador de este conocimiento y el fabricante del medicamento como receptor y, en particular, a una serie compleja y numerosa de actividades, típicas de una empresa farmacéutica. La aceptación mutua, sincera y convencida por ambas partes de una serie de directrices que se describen en cuanto al desarrollo del producto, la fabricación, las especificaciones, el desarrollo analítico y el registro farmacéutico debe cumplir dichos objetivos

Palabras clave: Tecnología farmacéutica, transferencia de tecnología, lineamientos

1. Introduction

In the area of pharmaceutical industry, investments in innovation show a well-known increase as a consequence of a suitable financial situation that becomes apparent in an important economic growth and a larger willpower to seize the opportunities offered by a globalized market.

Therefore companies must be able to evolve. Evolving means continuous change that is based on innovation and the assurance of competitiveness which only can be achieved when all the company's activities are carried out in the best possible way and showing a particular interest in its daily and continuous improvement in R&D and manufacturing strategies.

By this way, the company is enabled to leadership in its business areas, dedicating itself to carry out those activities where it disposes of a high degree of excellence. It will contract out others that a purveyor can do more efficiently for them.

2. What does a technology transfer policy mean ?

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) [1] 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 externalisation comes into play as an opportunity entailing the delegation of activities out of the company as well as cessation of human resources and materials. This concept or necessity is supposed to respond to a series of weak points concerning drug development strategies fixed in this article to be either reinforced locally or outsourced like these

- Development management structure proves insufficient. No management educational plans in executive teams
- Lack of equipments and infrastructure. Poor confidence in R&D know-how
- Lack of introduction of Good Laboratory Practices, GLP, [2] & Good Manufacturing Practices, GMP, [3] 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 jointventure 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 [4]. Although an a priori prevision results difficult, the outsourcing degree will be rather high in the area of development due to the particularities of this activity.

In order to realize one of this kind of outsourcing, the companies observe the organizations that carry out potentially interesting research activities. In this sense, the development centres are expected to realize the activities on the same quality level and complying with the GLP and GMP guidelines, which is of fundamental importance for assuring an optimal level of operating and a strict quality assurance of the tasks established. The concept of technological surveillance proves to be an important strategic activity in the development policy of innovative companies.

For this reason it seems convenient to point out the following aspects to take into account at the moment of outsourcing development functions to one of those purveyors.

- Experience in the business sector. It has to demonstrate a reputable experience
- Cultural compatibility. It should belong to the same geographic region
- Confidentiality. It should be guaranteed by signing a secret agreement
- Relations with other institutions subcontracted in turn. Application of the same rules as in the main contract.
- Financial solvency. Accreditation by a company specialized in this kind of audits.
- Technical qualification. Follow-up of a quality plan concerning facilities, equipments, staff and procedures.

So a technology transfer policy in drug development can be realized as well in any direction development unit – production facility as well with new products, licensed ones or even already existing ones, concerning either the whole procedure or a part of it as it is shown in Figure 1

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

Formalizing the technology transfer policy can be expected:

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

By other hand, the drug production facilities are concerned by technology transfer as they are increasing their production capacities working for other companies. This implies an excellent opportunity for companies with either low used installations or equipments with a degree of exploitation of not more than 50 % of their maximum capacity or specialized companies with own procedures and technologies covering market gaps.

3. Planning a pharmaceutical technology transfer

A procedure of technology transfer from a knowledge centre to a secondary production plant is described next. It implies three phases: the beginning, the transfer and the conclusion. Each one has to be achieved in a documented manner.

3.1. Step One (Beginning)

At the beginning there has to be an agreement or a request between donor and receptor sides concerning the manufacturing of a new product, bulk ware or finished product.

The receptor side is to appoint a technology transfer director who should come preferably from the department of quality assurance having however a regulatory affairs background.

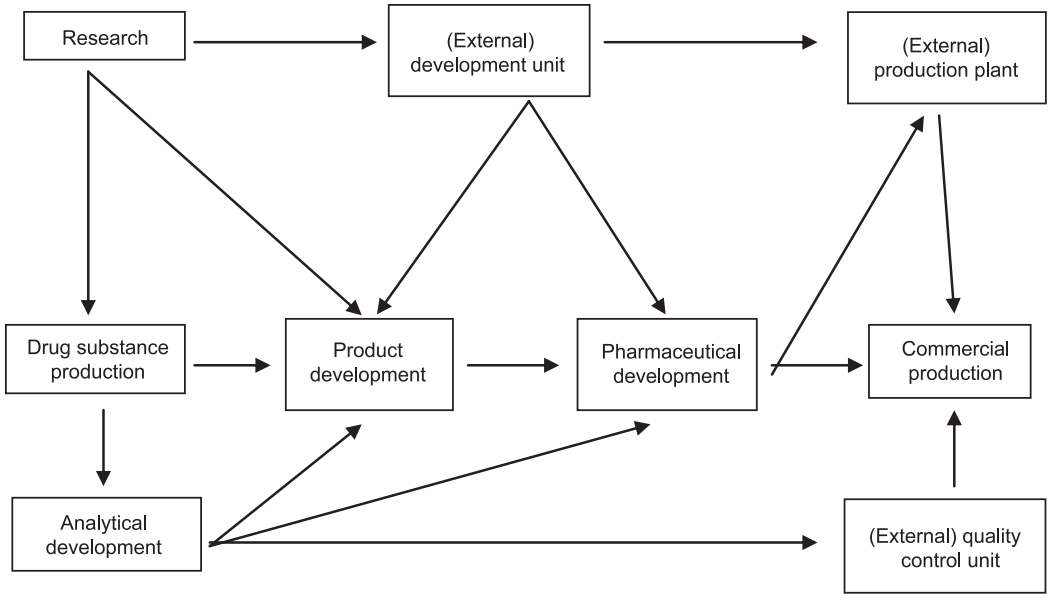

Fig. 1. Working directions in the R&D and manufacturing processes of drug in order to carry aou a Pharmaceutical Technology Transfer plan.

He should call a meeting between the representatives of both the donor and the receptor sides, so those mentioned by way of example in Table I, in order to begin the technology transfer process identifying the issues in relation to the product to be transferred.

3.2. Step Two (Transfer)

The production, the packaging, the control and those are in relation to the product quality like the achievement of the process and health and environmental protection follow a defined plan agreed by both sides. The said plan is to be outlined by the technology transfer director and negotiated with the representatives of both sides. It sets up the framework in which the technology transfer process will take place. Therefore it has to be designed to measure in order to meet the requirements of each particular case. It should especially establish key events and the dates of important revisions and final reports by means of a chronogram. The actions that are to be realized in order to finish satisfactorily the technology transfer should be included in a list.

There should also be an approved production procedure, constantly audited, that takes into account the receptor side's characteristics in each phase of the technology transfer of the project.

The technology transfer director of the project may manage and documentate its progress organizing meetings and inspections.

There have to be specified persons who dispose of an appropriate level of responsibility for authorizing each important step of the whole technology transfer process.

In order to achieve an appropriate technology transfer by both the donor and receptor sides, there is offered next a series of requirements to follow and to complement concerning:

- Product development phase: covering items like
  - Active Pharmaceutical Ingredients: Synthesis, Suppliers, Pharmacopoeial and Scientifical data (Table II)
  - Pharmaceutical Development: Formulation, Manufacturing, Quality, Stability and Bioavailability and Bioequivalence (Table III)
- Specifications: Quality of Starting materials, Intermediate products and Finished products and Packaging materials (Table IV)
- Manufacturing procedure: Facilities, Equipment, Documentation, Quality and Production (Table V)
- Analytical development: Methods, Validation, Samples and Equipment (Table VI)

In the same way the most relevant aspects concerning safety of starting materials, intermediate and final products have to be defined and assured implying usually the following aspects:

Table I. Business units of donor and receptor sides implicated in a technology transfer process

Development Unit	Production Site
Research	Industrial logistics
Pharmaceutical development	Business development
Analytical development	Technical direction
Quality assurance	Marketing
Regulatory affairs	Pharmaceutical development
Operations Management	Production
	Engineering and maintenance
	Quality control
	Quality assurance
	Safety
	Regulatory affairs

Table II. Active Pharmaceutical Ingredients

Definition of synthesizing procedure for the active substance: — Method — Definition of critical parameters — Apparatus used — Validation of the procedure
Details and state of suppliers approval
Certificate of conformity with the respective pharmacopoeial monograph
Preformulation data: — Chemical characteristics: structures, salts — Physico-chemical characteristics: Solubility, crystal properties, particle size, hygroscopicity, incompatibility, stability, etc. — Biopharmaceutical data — Relevant pharmacological and clinical data of interest

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Table IV. Specifications

Definitions and specifications (starting materials, intermediate and finished products):
— Physical parameters
— Chemical parameters
— Pharmacotechnical and functional parameters
— Microbiological parameters
— Unequivalences
— Expiry date
— Storage conditions
— Details and state of suppliers approval
Packaging (components, design and actual package)

Table V. Manufacturing procedure

Facilities (environmental conditions, liquids and gases, maintenance, cleaning procedures, water production, etc.)
Equipment (identification, qualification, cleaning, maintenance, etc.)
Flow charts
Batch records
Control of changes
Manufacturing yields
Recycling
Analytical results
Batch release
Withdrawals
Modifications in order to facilitate other industrial scaling-up
Stability studies (real time / accelerated)
Usual experience
Summary of the technology transfer reports towards other companies
Economic studies

Table VI. Analytical development

Summary and justification for the development of analytical methods
Final analytical methods (batch release and expiry date) and validation for starting materials, intermediate and finished products, known impurities and degradation products
Evaluation of the results and their statistical exploitation
Sample taking methods
Apparatus (identification, qualification and calibration)
Characterization of analytical standards
Usual experience

- Identification of risks
- Appropriate measures
- Manipulation and storage
- Exposition control and staff protection
- Stability and reactivity
- Elimination
- Transport
- Environmental toxicity

Because of the critical importance for the future commercialisation of the product, the regulatory aspects are already expounded in each section described previously. Nevertheless, the receptor side has to be informed about everything in relation to existing patents and their impact on production procedures, drug master file, types of demands for pharmaceutical commercialisation, industrial agreements as well as specific local restrictions and stability studies.

3.3. Step Three (Conclusion)

The technology transfer director of the project is to call a meeting of all the persons in charge of the previously described steps, reaching an agreement on a list of actions to undertake and establishing the respective dates for the conclusion of the technology transfer process.

After these actions being completed, a final revision will take place and the issue of a final document will confirm that the technology transfer process has been concluded agreeably. Thus it is to demonstrate that the pharmaceutical quality of the product in question is not adversely influenced.

Said document has to fulfil the requirements of the donor side. Its signing constitutes the final act and entitles the receptor side to sanction future changes concerning the procedure. The document is to be ratified by the departments of quality assurance and regulatory affairs of both sides.

During the beginning and the transfer process the responsibility for controlling changes in the procedure corresponds to both sides, but the donor side maintains all its authority to sanction them. At the end of the technology transfer, the authority to sanction changes goes over to the receptor side. The donor side commits itself to declare any modification of importance.

A bad transference will indicate analytical or manufacturing failures and an excessive effort on the donor and a lack of technical comprehension for the personnel belonging to the recepto. On the contrary, the suitable strength both of the product and the process and a high sensibility in the facilities of the receptor will denote a satisfactory transference.

Definitively, the increasingly usual not coincidence of the centres of development of drugs with those of its manufacture forces to design systems of transmission of the knowledge to avoid sensitive economic losses and of competitiveness derived from a bad management concerning, even, the quality of the pharmaceuticals.

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