



REVIEW ARTICLE

RESEARCH, DEVELOPMENT AND TECHNOLOGY TRANSFER FOR INDUSTRIAL SUSTAINABILITY

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Abstract

Industrial development and continuity, which are indispensable for countries, depend on sustainability, which can be defined as Permanent Capability. In the basic steps of industrial sustainability, there are social, economic, and environmental factors. ISO 14001, 14004, 14005, and 26000 regarding sustainability are important standards in this field. Research & Development and Technology Transfer are among the main factors that foster industrial development and continuity. Research & Development has three basic steps; it includes basic research, applied research, and experimental development, and its most important output is innovation. The industrial application of innovation or its transfer is possible with Technology Transfer, and this systematic process consists of five steps: providing the most suitable technology source to determine the most suitable option, selecting the optimum technology, having the necessary equipment and license, transferring knowledge and experience, and ensuring maximum benefit. Training and measurements are required to manage the process and for the internalization of the transferred technology. In this context, this review provides a basic and brief view of Research & Development, Technology Transfer, and Sustainability concepts and interactions, which are critical for the pharmaceutical industry.

Keywords: Innovation, Research Development/R&D, Sustainability, Technology Transfer/TT.

INTRODUCTION

Intellectual capital is among the indispensable elements in the development of today's various industries. Adaptation of existing or new information to the existing product or a new product development process can be considered as the output of Research & Development (R&D) in the field of product development. In terms of product, R&D is a development, which provides scientific and technological knowledge and design in the field with creative works carried out on a systematic basis, environmentally compatible product design or software activities to achieve an improvement for the knowledge of culture, human and society's knowledge and design for new processes, systems and applications. That can be defined as activities that focus on uncertainty and outputs which are original, experimental, scientific, and technical¹. A basic and brief view of Research & Development, Technology Transfer, and Sustainability concepts and interactions, which are crucial for the

pharmaceutical industry and researchers, is presented in this review.

Research & Development and Technology Transfer Three main activities that are indispensable for R&D are basic research, applied research, and experimental development. Sharing technological knowledge and competencies is essential in terms of time and cost in the development and sustainability of the industry. Transforming R&D into a product within the innovation process and securing intellectual property right can be given as the basic elements of transfer of technology^{2,3}. Technology Transfer (TT) can be defined as services that cover the commercialization process of innovations and innovative products as a result of scientific research from the beginning to the end. Stages of a successful TT can be briefly indicated as^{3,4}:

- To have a wide range of options and to have a network of technology resources to determine where the most suitable option for needs is and to ensure the development of this network,

- Making the selection by determining the option that offers the required technology in the best way,
- Negotiations required transferring technology not only with equipment or with licenses, but with the knowledge and experience, which contains managing the transfer process in a way to benefit from the transfer process at the highest level. It can be summed as experiencing an effective learning process in order to "internalize" and develop technology after it is transferred.

The institutions, which are intended to be implemented a transfer of technology initially need to be evaluated and trained in terms of adaptation speed to technology, technical sources, education level and technical capacity of employees, existing infrastructures, financial and commercial systems that play important role in technology transfer. In the application of new technology in the production area, science, organization, and management are necessary, and know-how for the application of theoretical or practical techniques must be involved in this process. Among the reasons for developing new products in various industries are changing needs, consumer demands, the discovery of new substances, legal changes, improvement of market position and share, which are the orientation towards R&D and TT. Below indicated three activities are the steps that should be applied in their order for R&D activities and development of today's industries^{1,2,5-7}.

Basic Research

It is the step of obtaining new information about what lies under the phenomena and observable situations that are based on theoretical or experimental studies. A specific application or use is not intended to be considered.



Applied Research

In the applied research step, it is aimed to produce original knowledge. A step that contains a direct original and practical purpose as the main goal.



Experimental Development

This step is the systematic work step to create new processes, systems, services or significantly improve those already produced or created to produce new materials, products, circuits derived from existing knowledge-based research and/or practical experience. In the initial stage of technology transfer in organizations, indicated pre-assessment parameters below need to be considered, and the stages need to proceed.

- Speed of adaptation to technology and technical sources
- Education level
- Technical capacity of the employees
- Existing infrastructures
- Finance and trade systems

Stages of a Successful Technology Transfer

To have a wide range of options and to have a network of technology resources in order to know where the option best suits the needs and to ensure the development of this network.



Determining the option that offers the required technology in the best way and making the selection accordingly.



Conducting the necessary negotiations to transfer the technology with the knowledge and experience it contains in addition to the equipment or license.



After the agreement, ensuring that the transfer process is managed in a way that will benefit from it at the highest level.



An effective learning process stage to ensure that technology is "internalized" and developed after it is transferred.

Innovation

Among the internationally accepted sources for the definition of innovation, the Oslo Guide, which is an international guide to information gathering and guidance on innovation that has been published jointly by the Organization for Economic Co-operation and Development of the European Communities-OECD and the Statistical Office of the European Communities-Eurostat indicates that innovation is a new or important modified product, which can be a good or a service or a process that can be a new marketing method or organizational procedure in business practices workplace organization or external relations. The innovation for the product mentioned a new or improved product or a process, which is significantly different from the former product or process that is available. The production of new ideas with innovation and the replacement of these ideas to a new product, process, or service duration, the growth of the national economy dynamics and the increase in employment, as well as the provision of profitability for the innovative business field⁵⁻⁶. An another guide of OECD that set a standard in research and experimental development indicators constitutes the basis of OECD scientist and technology policies in the formulation of scientific science and technology policies, and this guide has been continuously updated by taking advantage of the experiences of OECD countries. As of the scope of this guide, the subject of the measurement of the financial and human resources allocated to research and experimental development⁷. Another complementary guide to examining with the OECD is the Canberra Guide. The purpose of this guide is to provide an appropriate platform for

gathering data, preparing profiles, and current series on human resource stocks and in science and technology⁸.

Sustainability

From sustainability to induction, Sustainable Development has been shaped as a method to increase the level of economic growth and welfare by protecting the environment and human life quality. Sustainability is seen as an element that industrial components should primarily include in their strategic plans for the future, which plays a fundamental role in all industries⁹. In a product cycle, social, economic, and environmental factors constitute the basic steps and business model of sustainability^{9,10}. A common international standard for sustainability has not yet been published, and ISO 14001, ISO 14004, ISO 14005, and ISO 26000 are among the important standards in this field¹¹⁻¹⁴.

Corporate social responsibility and sustainability reporting have become mandatory in some countries. The increase in the population and the welfare level around the world and the consumption of products are in parallel products are in parallel with the planning and monitoring of the increasing consumption within the framework of sustainable development. The following methods are evaluated in terms of sustainability through the chemical industry, which is also a part of the pharmaceutical industry, which has relations with many industries. In the industrial cycle, social, economic, and environmental factors constitute the basic steps and industrial model of sustainability.

- **Environmental Aspect:** The use of renewable resources in order to protect natural resources and balance should not exceed renewal rates-rates.
- **Social Dimension:** It requires society to adapt and work towards a common goal.
- **Economic Dimension:** Financial development and continuity are made possible in line with social and environmental sustainability.

Chain and Interactions in Product Development

In product development, at first, vision, goals, roadmap, metrics, and the team need to be determined as components of the Development Strategy. Product development identifies all stages of the process of bringing a product to the market. The components of the process can be listed as the definition of desired product, targeted population and need for feedback, creating a pre-design, laboratory-scale manufacturing, manufacturing the product and releasing, marketing, and consumer feedbacks. There is a need for a professional product management team as strategic directors of the process. Product development is a broad process, which involves a coordinated effort of many teams from technical to financial experts. Components of product development are mainly listed as; product management, design, development including manufacturing, testing, and quality assurance, marketing, including shipping and distribution¹⁵.

Challenges encountered during product development differ according to the manufacturing activity and licence type of the pharmaceutical product. In today's concept there are three types for commercial pharmaceuticals and those are; reference (original) product, generic product, and biotechnological

product¹⁶, of which their definitions are as follows. Reference drug: The first product developed by the innovator company and released to the market under patent protection¹⁷. Generic drugs: Proven by scientific studies to have the same properties as reference drugs, thus providing the same treatment on the patient, and are offered for sale after the protection period of reference drugs expires. A generic drug has the same efficacy, quality, and safety as its reference¹⁷. Biotechnological drugs: Containing biological sources or one or more active substances derived from them. It is obtained using living systems, usually by reproducing a protein in a living cell (such as a bacterial or mammalian cell)¹⁸.

The R&D and TT processes of these three products and the challenges that may be experienced differ from each other. However, no matter which pharmaceutical product group is the case, the common challenge in the R&D and TT process is cost. Costs need to be kept as low as possible. For this reason, the preliminary discovery and pre-formulation process, which is the first stage of R&D, aims to achieve the most efficient result with the least possible expenditure. However, the factors affecting the costs for these three groups of pharmaceutical products of which R&D processes work with completely different mechanisms are also various. Thus, R&D and TT processes should be handled separately for each product. The biggest challenge encountered in the R&D process of reference drugs is product toxicity¹⁹. The International Center for Medical Research-CMR reported an average success rate of 4.9% from the first dose of toxicity to market approval in the Pharmaceutical R&D Factbook 2014²⁰. This average value has also been reached by different studies²¹. Another important challenge is the efficiency problem. Significant investments are made in the period from the discovery of a molecule to its commercialization. However, one of the biggest risks is that the effectiveness of a new drug at any stage of the R&D process cannot be seen at the expected rate. There are many examples where a drug was found to be effective in pre-clinical studies but was not effective in clinical studies, or failed in phase 3 despite successfully results in phases 1 and 2 of clinical trials. Other problems encountered in¹⁹:

- Reference drug development is the inadequacy of pre-clinical models used in exploratory research and pre-clinical testing.
- Insufficient pharmacokinetic data, reliability problems obtained.
- The complexity of the biological mechanism and clinical trial design encountered in drug targeting or drug development for the treatment of chronic diseases.
- The lack of knowledge of small companies that generally carry out R&D the process.

The challenges encountered in the R&D and TT process of generic products are relatively less compared to reference products. For generic drugs that do not require pre-clinical and clinical studies, the main determining factor is the characteristics of the reference drug. A generic drug can be approved by commissions

if it has similar pharmacodynamic and pharmacokinetic properties to the reference product¹⁷. It is sufficient to carry out studies in which it is compared with the reference product (critical parameters such as dissolution, solubility, dispersion, etc. are checked) and that it is bioequivalent to the reference product. Since there is an existing example, the R&D process can progress more easily and quickly. The biggest possible problem is the legal processes that may occur depending on the patent protection of the reference product. If the patent protection period of the product has expired or if the patent can be broken with an innovative invention step in product development (except for indication patents), such a problem will not occur. To reduce costs, the main goal should be to reach the reference product specifications with the least possible formulation during the pre-formulation period. While the R&D and TT processes of biotechnological drugs have the main problems of both reference and generic drugs, there are also special cases. Some of the active ingredients in biotechnological drugs produced from biologically sourced materials are proteins, insulin, growth hormone, and erythropoietin, which are already present in the human body. The active ingredients of biological drugs are larger and more complex than the molecular structure of the active ingredients of non-biological drugs¹⁸. Since biotechnological drugs are produced from living cells, their properties are mainly dependent on the conditions of the production process. For this reason, they are called "process products". Even small changes in production can alter the final product. For this reason, the production processes of biological drugs must be well designed, robust, reliable, and fully controlled. It is the manufacturing process itself that gives biological products unique properties. It is the product group in which the scale-up process from the R&D process to the production line is the hardest to settle. Production with living cells directly affects the efficiency of the scale-up process. On the other hand, since they are process products, the minor change that may occur in the process changes the quality of the product and, therefore, the product's effectiveness. The high risk of contamination and the death of living cells in possible contamination is the most undesirable situation. The loss of a cell line, on which the entire production process of the drug is based, means that all processes related to that product start from the beginning. This means both a serious waste of time and a high cost. Manufacturers maintain primary cell lines in order to minimize all possible problems in such a situation. Thus, they can restart their production processes from an intermediate step. In biotechnological drugs, there is no generic drug concept. A biosimilar product that is frequently encountered and mixed with a generic drug means a biological product that has been developed to have a high level of similarity to an existing biological product (reference product). Biosimilars are not the same as generic drugs, which have simpler chemical structures and are thought to be exactly the same as reference products. Since biotech drugs are process products, biosimilars can only be "similar" to the reference product. It is accepted that there may be

some differences between two products due to different processes, and the process itself is defined as a "product". A biosimilar and its reference product are not structurally identical as they are produced by different cell lines and production processes, but the products are highly similar. There are no significant differences in terms of quality, reliability, and effectiveness. The problems experienced in the R&D and TT process of biosimilar products are the same as the biotechnological reference product. Since it has to be similar to the reference product in terms of quality, reliability, and effectiveness, the criteria it must actually meet are much more stringent^{22,23}.

Finally, in addition to the above drugs, a group of botanical products aimed at improving or protecting human health also take an important place in the field of R&D, and regulatory requirements differ from country to country. R&D and TT on botanical drugs is strongly influenced by their goals, driven by safety and efficacy, and also have challenges on stability²⁴.

CONCLUSIONS

In various industries, for reasons such as changing needs, consumer demands, discovery of new substances, legal changes, improvement of market position and share, there is a need for new product development and therefore R&D and TT. It is stated that sustainability will have many industrial benefits, effective planning in resource use, raw material, energy use and reduction of waste materials will reduce costs and the various product-focused industries will directly affect sustainability. The application of the sustainable development method in the health related industries will positively advance the social, economic and environmental impacts of the societies.

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AUTHOR'S CONTRIBUTION

KOCA M: study design, writing original draft. **DURGUN ME:** literature survey. **ALGIN YAPAR E:** critical review. The final manuscript was read and approved by all authors.

DATA AVAILABILITY

Data will be made available on reasonable request.

CONFLICT OF INTEREST

None to declare.

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