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Using TRIZ to Accelerate Technology Transfer in the Pharmaceutical Industry

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Abstract
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. Challenging, seemingly impossible problems arise at all of these interfaces. Case studies demonstrate that TRIZ can solve these problems, and speed the progress of new pharmaceuticals to market. The TRIZ concpts of increasing ideality, elimination of tradeoffs, and elimination of inherent (physical) contradictions are applied to the improvement of testing, reduction of toxicity, and scale up for production in several areas of the pharmaceutical industry.
Keywords: TRIZ, TRIZcase study, pharmaceutical industry, technology transfer

1. Introduction

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. Challenging, seemingly impossible problems arise at all of these interfaces. Figure 1 shows the time scales and the financial investment in each of the 4 phases of drug development. See Mlodozeniec, 2004 (1) and (2).

1.1 The New Drug Application Process

The New Drug Application (NDA) is the full record of the development and testing of the drug, presenting the case that it is ready for human use, and including validation of all test methods, and proof that the medication produced by the full scale, commercial production system is the same as the medication that was developed and tested in the clinical trials. See ISPE 2003 for detailed descriptions of the requirements in each phase.

The process from beginning of research to release of the drug may take anywhere from 5 to 20 years. There are 2 reasons that the pharmaceutical companies want to accelerate this process, which we call the business and the humanitarian reasons:

1. Business: The part of the drug's lifetime during which it is covered by patents is the most profitable part. The longer the development time takes, the shorter the available patent life.
2. Humanitarian: The sooner the drug is brought to market, the more people will benefit from it.

The use of TRIZ problem solving methods to accelerate the process will help pharmaceutical companies accomplish both goals simultaneously.

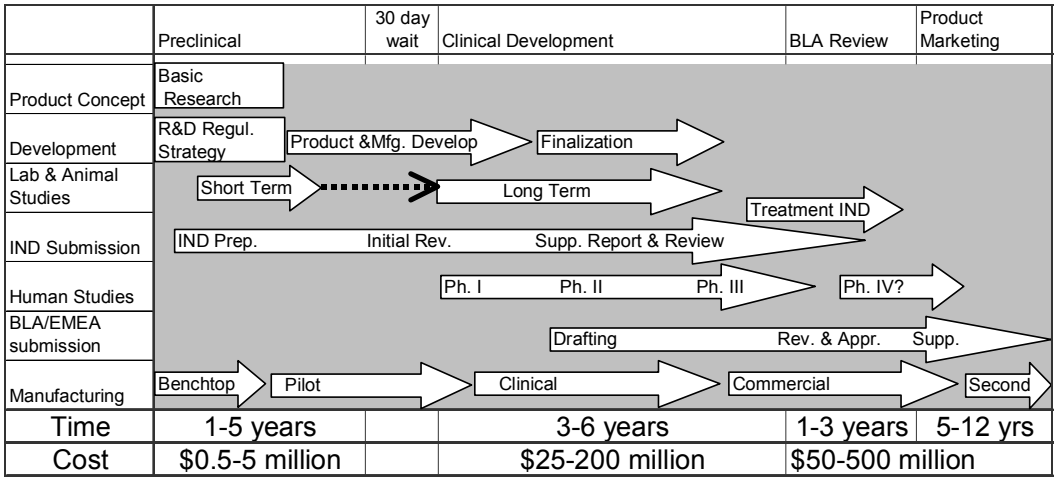

Figure 1. Typical New Drug Development time scale. Regulartory reviews refer to the FDA, the US Food and Drug Administration. EU systems are similar. See Mlodozeniec 2004 (1) and (2).

1.2 Selection of Case Studies

Technology transfer in the pharmaceutical industry refers to the transitions between the 4 primary phases of the New Drug Development process:

1. Drug Discovery
2. Product Development
   2.1 Delivery method
   2.2 KADME (Kinetics of Absorption, Distribution, Metabolism, Excretion)
3. Clinical Evaluation
   3.1 Pre-clinical toxicity evaluation
   3.2 Animal and human studies
4. Full scale commercialization ~ Technology Transfer
   4.1 Active Pharmaceutical Ingredient (API)
   4.2 Drug Product (Dosage Form or Delivery System)
   4.3 Analytical Methods

In each phase, researchers attempt to optimize five attributes:

1. Flexibility
2. Cost
3. Dependability
4. Innovation
5. Product Quality

The TRIZ case studies have been chosen to illustrate improvements in all attributes in stages 2, 3, and 4 of the New Drug Development process. Stage one is equally subject to the use of TRIZ, but the authors have not been working in that area and have limited this paper to their own experiences with TRIZ and technology transfer.

This paper is a continuation of the work presented by Domb and Jacklich in 2003 demonstrating that the use of beginner-level TRIZ techniques can have major impact on development of new technology. Several of the cases could be analyzed in terms of the patterns of technical evolution, but that analysis is not included since the work was done using only ideality, the 40 principles (elimination of technical or tradeoff contradictions), and the separation principles (elimination of physical or inherent contradictions). See Rantanen and Domb, 2002, for discussions of the basic TRIZ techniques.

2. TRIZ case studies in technology transfer

2.1. Improve test models

In the pre-clinical test phase of New Drug Development, it is necessary to demonstrate that the medication will be both safe and effective for use in humans. Traditionally, testing has been done in animals. Numerous tradeoffs have been required to select the animal species to be used for a particular test. It should closely match the characteristics of the human body, particularly for the organ system being studied, but cost issues require that the animal be small and easily cared for. The need to do a statistically significant number of tests makes the cost issues even stronger, leading to the popularity of laboratory rats, mice, and rabbits as test animals. If the animal is not subject to the same diseases as humans, it may be necessary to do the toxicity/safety tests on one animal and the effectivness tests on others.

2.1.1Eye medication and rabbits

Rabbits have been used to test the irritation index of both medication and consumer products for many years, and to test the rate of absorption of medication. But, rabbits have a very different blink rate from humans, and a different pattern of eyelid shear during blinking. Making them an imperfect test model, since blinking is a very important mechanism for distributing tears in the eye.

The diffusion flow cell has now replaced rabbits. The diffusion flow cell is an assembly of monolayers and bilayers of cultured human cells that have the exact properties of the human eye. They make it possible for researchers to isolate the effects of tears and of the boundary layers between the parts of the eye, while entirely eliminating the complexity of dealing with animals. This solutions demonstrates the use of 2 of the 40 principles for problem solving:

Principle 17: Change Dimensionality
Principle 27: Cheap Disposable Parts

2.1.2. Vaginal microbicide development, rabbits, and baboons

Rabbits have also been used to test products for human vaginal use, and they are also an imperfect model for this use, since the rabbit has a vaginal pH of 7, while the human has a

pH of 4.5. Consequently, medication that matches the human pH is severely irritating to the rabbit. The mismatch can also result in medication that kills the beneficial lactobacillae, which then allow yeast infections to flourish.

The alternative to rabbits has been baboons. They are a much closer match to humans, but they are extremely expensive to acquire, and to care for.

The diffusion flow cell again is the solution, since it can be made from the specific cells of the organ being tested, and will therefore have exactly the right parameters for the test.

2.1.3. Skin: trans-follicular kinetics

During the pre-clincal phase of development of medication to be applied to the human skin, researchers need to determine the kinetics of the transport of the medication through the skin. Because of the high variability of the number and size of hair follicles on human skin, it has been difficult to isolate the trans-dermal (skin) and trans-follicular(through the hair follicles) effects.

Snakes have no hair! Snake skin is an excellent model for the hairless skin, and tests on snake skin can be used to isolate the trans-dermal and trans-follicular effects.

This solution demonstrates the TRIZ concept of using effects from another science combined with Principles 2 and 3:

Principle 2: Take out: Use only the necessary parts

Princkple 3: Local quality. Make the system have the exact properties desired.

2.2. Distribution

In the pharmaceutical industry, distribution includes the typical industrial activities of packaging, shipping, warehousing, retailing, etc., and also includes issues of customer use. The case studies demonstrate both.

2.2.1. Eye medication—assure correct time and dose

Eye medication is usually dispensed in liquid drops, since it is very easy for non-medical personnel (the patient himself, or a care giver) to dispense the proper quantity, by relying on the shape of the dispenser and the surface tension of the liquid. But, the time that the medication stays in the eye is unpredictable, since liquids drain into the cul de sac of the eye. See figure 2.

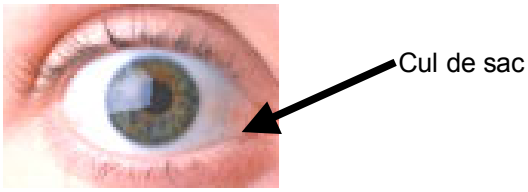

Figure 2. The human eye. Liquid medication drains through the cul de sac, and does not stay in the eye.

From a TRIZ perspective, this is a physical (or inherent) contradiction: <u>you want liquid medication but you don't want liquid medication.</u> The solution comes from the separation principles: separate liquid and not-liquid in time and in space. The solution is a formulation of the medication that is liquid in the bottle, and when being dispensed from the dropper, but which binds with the tears in the eye to form a gel when it contacts the tears, and is activated by body temperature. This could also be thought of as demonstration of Principle 35, Change Parameters.

2.2.2. Protect potency of proteins during shipment

Proteins are often difficult to ship in liquid form. They arephysically unstable, subject to aggregation container surface adsorption, easily damaged by temperature changes, and in general have short shelf life. The containers themselves are subject to breakage of walls and difficulty with creating a secure closure.

The solution to all these problems came from the application of the "itself" form of the Ideal Final Result: "The protein should protect itself during shipping." (See Domb 1998, Mann 2003 and Belski 2000). The solution is to freeze-dry the protein material, ship it in the dry powder form, and reconstitute it at the point of use. This solution could have come also from the application of Principle 35, or from use of the principle of separation in time, for the physical (inherent) contradiction: The protein should be liquid (for easy use) but it should not be liquid (for easy handling and shipping.)

2.3. Scale up for full commercialization

"Technology Transfer" refers to the initial stage of transferring the drug system out of the laboratory, into pilot-scale plants, the intermediate stage of transferring to full commercial-scale plants, and, if the product is successful, to secondary commercialization, which frequently involves transfer to numerous facilities in multiple countries. See ISPE2003 for discussions of the regulatory concerns in each of these transitions.

TRIZ applies to the technical and management problems encountered during each of these transitions, as demonstrated in the following brief cases.

2.3.1. Avoid foam problems

When liquids are moved from one station to another (such as a reactor to a storage tank to a mixing tank, etc.) turbulent flow at an air interface can lead to the formation of foam, and the non-scalability of flow parameters makes the occurrence of foam unpredictable. A very simple TRIZ solution does not solve the problem of foam creation, but it make foam not cause problems for downstream processes: apply Principle 13 (do things in reverse) and extract the liquid from the bottom of the tank, to get pure liquid without any foam.

2.3.2. Improve medication uniformity by electrostatic deposition

Although pill production by compressing powder is a well-established technology, there are many drugs that require higher accuracy and uniformity than the powder compression method can provide. Considerable improvement in uniformity has been achieved by electrostatically depositing the material on a continuous web of edible material.

The TRIZ pattern of evolution "Object Segmentation: Divide the object into smaller and smaller parts, and eventually replace the object with a field" would have predicted this solution. The "Beginner TRIZ" methods from the 40 principles, using Principle 28, "replace mechanical objects with fields" was used.

2.3.3. Reduce production loss and improve product quality using continuous testing instead of batch testing.

Batch testing for quality can be extremely expensive, because a bad test may require either extensive re-testing, or discarding the entire batch. Decisions about batch intervals are subject to trade-offs between test interval, test cost, and cost of scrapping bad batches. By replacing the batch test with a continuous scan by means of FTIR (Fourier Transform InfraRed Interferometry) and by doing continuous statistical process control analysis on the data, production discrepancies can be detected immediately, and the rejected material reduced to a very small fraction of a batch.

This is another example of the improvement of ideality (same benefit with less cost and less harm) by means of replacing mechanical, batch testing with continuous electromagnetic testing and statistical analysis.

3. Conclusions

Case studies never "prove" anything. This collection of case studies from technology transfer in the pharmaceutical industry is designed to demonstrate that the skills of beginner-level TRIZ can make substantial contributions to the problem solving that is necessary to move a new drug along the exhaustive pathway from basic research to clinical research to full commercialization.

For pharmaceutical audiences, this may answer the question: ***"Does TRIZ work in my environment?"***

For TRIZ audiences, it may answer the question: ***"Can I start using TRIZ when I've just begun learning it? "***

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