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J. No. x599
May 10, 1999
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TECHNOLOGY MANAGEMENT OF THE DEVELOPMENT OF STATISTICAL METHODS AND MODELS FOR STANDARDIZED PRECLINICAL STUDIES

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TECHNICAL REPORT
IMM-REP-1999-07

IMM

Abstract

This paper is a part of a Ph.D. thesis concerning "Statistical methods and models for standardized toxicological and safety pharmacological studies". The research project will in this paper be viewed in a technology management perspective.

The technology management philosophy and theory is used to understand how the project fits into the business strategy of Novo Nordisk A/S and how it is possible to optimize the effectiveness of the company.

The company is introduced and its strategies explained, followed by a description of the project and how the results of the project can optimize the effectiveness of the development process. The process of developing a new technology knowledge within Novo Nordisk A/S is described by an actor-network model and afterwards it is analyzed by a socio-cognitive model. Finally, the method of developing a standard method and recommendations for implementation are discussed.

Lyngby, May 4th 1999

Contents

1 Introduction

The project is a joint venture between the Danish pharmaceutical company Novo Nordisk A/S and the Institute of Mathematical Modelling (IMM) at the Technical University of Denmark (DTU). It is granted economically by the Danish Academy of Technical Sciences (ATV) and Novo Nordisk A/S.

The purpose of the project is divided in two parts. The first and most important part is to standardize the statistical methods used to analyze pre-clinical data. The second goal of the project is to close the project by spreading the knowledge to the world and make other work with the new ideas. If the last part is not fulfilled we only have a suggest for a standardization that the company can use it self. It will first become a standard when it is accepted and/or used worldwide. Both parts of the project will be described and analyzed in this report.

The project group consists of seven persons. One statistician from Novo Nordisk A/S and one from IMM, two toxicologists and one safety pharmacologist, one data manager and one Ph.D. student. The group meets about once in a month.

The project was started the 1'*th* of November 1996 and will be finished in three years.

The term "technology" does in this paper refers to both "technology knowledge" because the Ph.D. project looks at new statistical standardized methods and to "a new drug" because that is one of the products the company develops.

2 A short introduction to Novo Nordisk A/S

The following information is from the companies home page [12] and can also be found in [8].

Novo Nordisk A/S was formed in 1989 by a merger of the two Danish companies Nordisk Gentofte A/S and Novo Industri A/S. Novo Nordisk A/S is a world leader in insulin and diabetes care and the world's largest producer of industrial enzymes. The company also manufactures and markets a number of other pharmaceutical and bioindustrial products.

With a net turnover in 1997 of DKK 16932 million, Novo Nordisk A/S is one of Denmark's largest industrial enterprises. As of 31 December 1996 the company employed 14175 people in 61 countries.

2.1 History

Nordisk Gentofte was established in 1923 by the Danish Nobel Prize winner, Professor August Krogh, chief physician H. C. Hagedorn, and chemist A. Kongsted. The basis for establishing the company was the right to produce insulin which Professor Krogh had obtained from the Canadian scientists Banting and Best who in 1922 were the first to produce insulin by means of an extraction process. Immediately prior to the merger, Nordisk Gentofte A/S was the world's third largest producer of insulin and one of the major manufacturers of human growth hormone.

Novo Industri A/S was established in 1925 as a producer of insulin. At the time of the merger, the company was the world's leading producer of insulin and the world's largest manufacturer of industrial enzymes.

2.2 Products

Novo Nordisk's two largest product areas are Health Care and Industrial Enzymes.

Health Care: Novo Nordisk A/S manufactures and markets a number of pharmaceutical preparations, the most important being: insulin and other diabetes care products, hormone preparations for gynaecological use, human growth hormone. Further, Novo Nordisk A/S, manufactures selected CNS preparations, and preparations for the treatment of blood disorders.

Throughout its history, insulin and other products and services for diabetes care have been the mainstay of Novo Nordisk Health Care.

Novo Nordisk A/S has pioneered virtually all of the improvements which have been made in insulin treatment since the discovery of the effect of insulin: The company was the first to introduce longer-acting insulins, first with pre-mixed insulins, first with highly purified insulins, first with human insulin and first with insulin pens.

In addition the company operates an internationally recognised diabetes treatment and research centre in Denmark, The Steno Diabetes Center.

Industrial Enzymes: Novo Nordisk A/S is the world's largest supplier of industrial enzymes. Around 50% of the world consumption of these enzymes are supplied by Novo Nordisk A/S. Enzymes are used in a wide variety of industries including: Detergent, starch, textile, brewery & wine making, sugar, leather, fat & oil, and pulp & paper. Research in the field aims at finding new uses for the existing range of industrial enzymes as well as finding new enzymes for new applications.

Enzymes are proteins capable of speeding up chemical processes which would otherwise run very slowly. Enzymes are so to speak nature's own catalysts which in many cases can wholly or partly replace aggressive chemicals used in industry today. An example of this is an enzyme which can reduce the use of chlorine in the production of paper.

2.3 Research and development

In 1996 the company spent more than 15.1% of the turnover on research and development. Major research areas include: Diabetes Care, Women's Health Care, Growth Disorders and Industrial Enzymes. More than 3000 of Novo Nordisk's employees are involved in R&D activities.

3 Project phases in Health Care Projects

In the rest of the paper only the Health Care area of Novo Nordisk A/S will be considered.

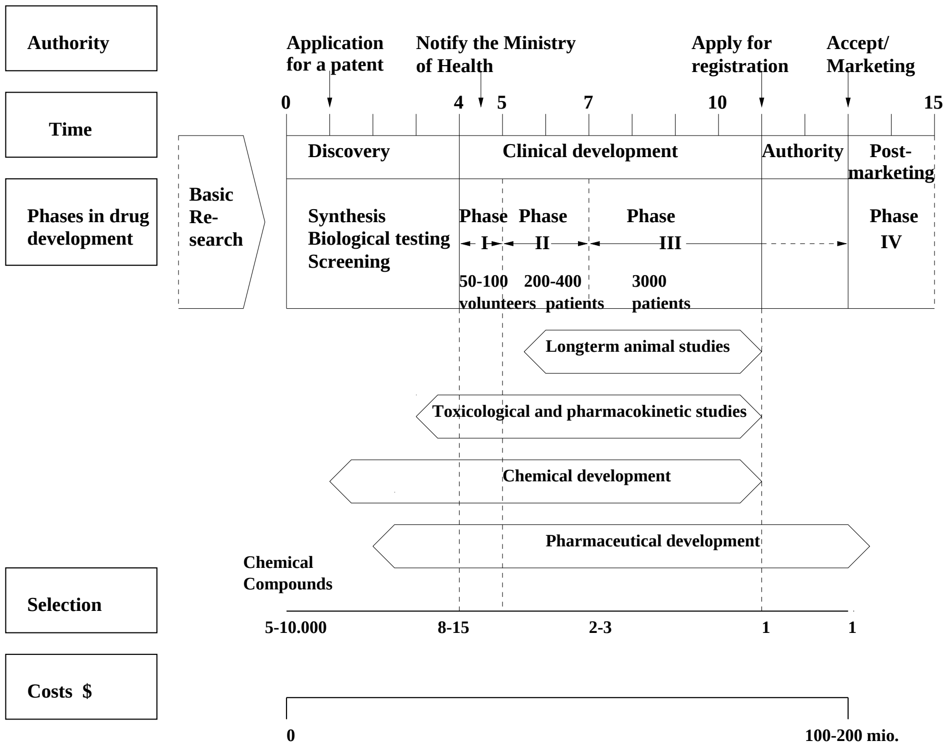

Figure 1: The process of discovery and developing new drugs at Novo Nordisk A/S.

The discovery and development processes in the Health Care area of Novo Nordisk A/S are shown in figure 1. Here the authorities involved in the project are listed together with the phases which the drugs are going through. Also the time it takes for the product to go through the different phases is given together with the selection process of the single final product. The cost for a new drug to be developed is shown in the end of the figure. In the following some comments will be given to the figure.

3.1 The developing phases

The phases in drug development are divided into a pre-clinical phase, three clinical phases, a registration phase and a post-marketing phase. The phases can be described as;

Pre-clinical
A substance which has shown positive properties in the laboratory is evaluated by pharmacologists and other professionals. The safety and therapeutic effect of the substance on animals is tested.

Phase 1
The substance is tested in about 50-100 healthy volunteers.

Phase 2
The first administration of the substance takes place in 200-400 patients for evaluation of efficacy and tolerance in short-term treatment.

Phase 3
The substance is tested in a large number of patients (about 3000 or more) for evaluation of efficacy and adverse events in long-term treatment.

Submission for registration
If the clinical trials have succeeded, applications for registration are submitted to the authorities in the countries where marketing approval is sought. The average time for the authorities to review an application for registration

is one to three years.

Post-marketing
If the authorities accept the registration file then the marketing process can start.

3.2 The Authorities

It is important to notify the authorities at the right times throughout the progress of development. Otherwise, the whole time schedule can be delayed because of special datelines that have to be met. Novo Nordisk A/S has a special department that takes care of all the communication with the authorities.

3.3 The time

Often different pharmaceutical companies begin the search for a drug to treat specific disease at almost the same time. Therefore, it is important for the company to decrease development time so it can be the first on the market and thereby gain the greatest market share.

Normally, it takes about 13 years before the drug is ready for post-marketing and has been accepted by the authorities. It is in the company's interest to cut that time down as much as possible without compromising the safety and the quality.

3.4 Selection of the final compound

Throughout the discovery phase the number of potential compounds decreases from about 5-10.000 to 8-15 which means that before the clinical development the number of candidates is down to less then 15. After phase I the number is down to 2-3 and hopefully one of them is the drug the company has been looking for with efficacy and thereby effect on the disease but with no adverse events what so ever.

3.5 Costs

It costs about 100-200 mio. $ to discover and develop a new drug. Hence the first 13 years is only dead loss. Hopefully the drug is able to pay for itself later on.

4 The business strategy of Novo Nordisk A/S

Porter [14] states that it is important for a company to have a business strategy for its possibility to survive. He states, that "The essence of strategy is choosing to perform activities differently than rivals do". This is indeed true for smaller companies which have a lot of competitors. For a company like Novo Nordisk A/S it is different because the firm possess a strong technology. The technology strength of a business is described by Erickson et al. [4] as "The technological strength of a business reflects the degree to which it has competence in, or proprietary control of, key product and process technology. It also reflects the level of investment to sustain key technologies and to invest in pacing technologies".

Novo Nordisk's strategy is build on the principles according to Porters suggestions "Strategic positions should have a horizon of a decade or more, not of a single planing cycle" [14]. The strategy of Novo Nordisk A/S is build on a company vision called "Vision 21" expressed as purpose, mission and the way to reach the goal. Vision 21 can be found e.g. on the companies home page [12] and is listed in the next section. The "purpose" of the strategy is the foundation for the whole company and it is planned to last for centuries. The "mission" is planned to last for between 10 and 100 years and the "ways to reach the goals" is what the company has to do today and over the next couple of years to secure it works in the right direction towards fulfilling the mission and the vision of the company.

With a business strategy build on Vision 21 it is possible for the managers at Novo Nordisk to change the "ways to reach the goals" every once in a while so that it still fits the overall vision of the company. In that way we have what Stacey [15] calls "a continuing, interactive game in which organisations and people are adjusting their strategies, changing the rules of the game as it were, so as to render themselves fitter for survival and success".

4.1 Vision 21

Purpose

- The business of Novo Nordisk A/S is to discover and market products which satisfy real needs - improving the way people live and work.
- Novo Nordisk A/S will find better ways to fight the burdens of disease and to provide sustainable biological solutions to industrial problems.

Mission

- Novo Nordisk A/S shall be the best in its businesses and a challenging place to work.
- Novo Nordisk A/S shall grow as an independent company making all important business, people, and policy decisions themselves.
- Novo Nordisk A/S shall pursue innovation in all its activities and aggressively build leadership positions in there markets.
- Novo Nordisk A/S shall become its customers' preferred partner.
- Novo Nordisk A/S shall deliver a competitive financial performance.

The company's way to reach the mission

Accountable
Each of the employees shall be accountable - to the company, his colleagues and himself - for the quality of the efforts, for contributing to the goals, and for developing the culture and shared values.

Ambitious
All employees shall set the highest standards in everything they do and reach challenging goals.

Open and honest
The business practices shall be open and honest to protect the integrity of the company and of each employee.

Close to the customers
All employees shall seek simplicity in all business processes, share information, and push initiative as close to the customers as possible to release personal energy and to constantly improve performance.

Ready for change
All employees must foresee change and use it to the company's advantage. An ongoing dialogue between management and employees shall ensure that personal training and development activities strengthen the company and secure the employability of the employees preferably within Novo Nordisk A/S.

Responsible neighbour
The company shall all over the world conduct its business as socially and environmentally responsible neighbours, and contribute to the enrichment of the communities.

4.1.1 The practical aspect of Vision 21

The company has done a lot to extend the employees knowledge of the Vision 21, because if people do not know the vision of the company and do not work in accordance with it the vision has no meaning.

The vision is listed and explained in company newspapers and videos but that does not insure that the employees understand how the mission effects them. To understand it you really have to work with it. This is done on department basis on seminars where all employees have to translate the vision and missions to their working area explaining how they can help fulfilling the company vision and mission by the way they act and work.

4.2 Health Care's business strategy

The strategy of the Health Care devision is described on the company's entranet:

In 1994 Novo Nordisk launched a new business strategy. Building on the commitment of Novo Nordisk's mission to be "best in our businesses and a challenging place to work", the strategy set the course for the company's development into the next century.

The essence of the strategy is to focus the company's activities on a few selected areas in which it has a competitive advantage and where it stands a good chance of building and maintaining leadership positions. As a result of the new strategy, several business areas, products and projects have been divested of or terminated during the last few years, including drugs for central nervous system disorders, blood-plasma products, and dietary supplements. This, in turn, has allowed that more resources be ploughed into Health Care's main business areas:

- Diabetes Care.

- Growth Disorders.
- Hormone Replacement Therapy.
- Coagulation disorders.

Discovery strategies

Health Care's discovery activities focus on two areas in which the company have a significant and sustainable competitive advantage:

- Diabetes Care.
- Therapeutic proteins.

In diabetes Novo Nordisk is already the world leader; the market is growing rapidly; the company has a major opportunity to win marketshare in the US; Novo Nordisk has insulin - which is likely to remain the ultimate diabetes drug for the foreseeable future; the company has the richest pipeline of diabetes projects in the industry and excellent delivery devices.

In therapeutic proteins the company has NovoSeven, growth hormone, glucagon and ASIS, which together represent major growth opportunities. Equally important, the company has well-positioned to capitalize on new opportunities arising from genomics:

- Novo Nordisk is skilled in identifying, purifying, formulating and producing proteins.
- Novo Nordisk has expertise in developing and producing delivery systems.
- Novo Nordisk has sales and marketing expertise in the specialist and hospital segments at which protein-based products are typically targeted.

Health Care's 10 strategic business objectives

To accomplish its mission of being "best in its businesses", Health Care focus its attention on the key value drivers of the business.

Health Care Management has singled out what it considers to be the most critical goals during the next 3-4 years. Named "Health Care's 10 strategic business objectives", they are derived from the findings of the company's Strategic Planning Process, and a shared vision of how the company's external operating environment will change over the next 10 years. The 10 strategic business objectives are meant to give guidance for priority-setting throughout the organization.

In the company newspaper Margaret Hunter [6] describes the expectations of the new adjustment to Health Care's strategy and quote Lars Rebien Sørensen which is member of the board of directors. Hunter [6] writes: Based on input from the strategic planning process last year, the chance of Novo Nordisk being among the most successful firms ten years in the future is "good," according to Lars Rebien Sørensen, "if we play our cards right. It will require that we carefully focus on areas in which we have significant and sustainable advantages, and that we use our resources very wisely."

4.3 Operational Effectiveness

Novo Nordisk A/S has an overall vision and strategy which all employees have to follow. The strategy is unique for Novo Nordisk A/S and makes the company different from other pharmaceutical companies. Porter predicts that a company can only outperform rivals if it can establish a difference in that it can preserve [14]. Therefore strategy means performing activities that are different from those of the rivals' or performing similar activities in different ways.

The company can improve its strategy by gain knowledge about its competitors. Johnson and Scholes [7] describes a method to identifying the organisation's competitive position and understand the positioning of the organisation in relation to the strategies of other organisations.

Besides a strategy, it is important for the company, to be able to reach its goals, to work with *operational effectiveness* as Porter also states. Operational effectiveness means performing similar activities better than rivals [14].

The aim of the Ph.D. project is to improve the company's operational effectiveness in relation to the research and development process (see figure 1. In the following the Ph.D. project will be described together with the projects influence on the company's business vision, strategy and operational effectiveness.

5 The Ph.D. project

This Ph.D. project only concerns the pre-clinical part of the development course (see figure 1), but of course is also effects the registration part, because if the registration authorities do not accept the work done in the pre-clinical phase then the time for filing can be delayed.

5.1 Background

Among others, The Japanese Ministry of Health and Welfare (MHW) has asked Novo Nordisk A/S for consistency among consecutive statistical analyses throughout pre-clinical registration files for new drugs (insulin, hormones etc.).

During the last couple of years before the Ph.D. project was initiated, a group of scientists at Novo Nordisk A/S have developed a decision tree for the statistical analysis of toxicity data from animal studies.

Unfortunately, the decision tree has been found to lead to inconsistencies as variables are often analyzed differently from study to study, from time point to time point and between genders. Furthermore, it does not contain a test battery for the analysis of the dose-response relationship, nor recommendations for the analysis of repeated measurements. Another shortcoming of the decision tree is that it does not contain recommendations for the statistical analysis of safety pharmacology data.

The Ph.D. project was initiated to overcome these problems. The purpose of the statistical work in the project is to evaluate existing basic experimental designs and matching statistical models in toxicity studies where statistical methodology has already been applied.

5.2 Objective of the project

The project have two important purposes. First of all it is important to find models for the pre-clinical experiments that depend on the nature of the actual studies and not only on the data and statistics available. The models have to be as general as possible and at the same time applicable so that it is possible to use them in a consistent way. The second purpose of the project is to get the method accepted worldwide. This is not a crucial goal because even if it is not accepted by other companies, Novo Nordisk A/S will still benefit from the project by shortening the developing time for new products.

Standardization is a compromise and thereby a political decision. We know that the best thing to do on short term, is to look at every single study and find the appropriate statistical analysis for those data. Thereby every single study will be analyzed with a unique method that fits the data optimal. This procedure demand a lot of time and resources but more important is, that we are not able to fulfill another purpose namely to compare results from different studies. By standardizing the statistical methods we may loose something by not using the most optimal method in the single study but instead we gain something very important when we are able to compare results across studies.

The project group has been put together so it should be possible to find a consistent method within the company. None of the members of the group are from outside the company. Hence, the standardization method that the group develop will mainly be a compromise of what the members of the group find important. Besides, the members of the group have experience from cooperation with actors from outside the company (contract laboratories, authorities, other medical companies). Thereby the group have a suggestion of what the outside actors are willing to accept of a standard. Furthermore it is important that the method developed is not represented to the outside actors as the final and only solution of the problem but only as a new scientificly correct method that solves the inconsistency problem.

5.2.1 Consistent statistical analysis

The purpose of the statistical work is to establish a "knowledge data base" where experimental designs and empirical knowledge about biological response determine the statistical model, and hence the statistical analysis. The following should be considered through the Ph.D. project:

- Transformation of data
- Distribution of variables
- Statistical tests for outliers
- Statistical tests for homogeneity of variance
- Statistical analysis of single and correlated variables
- Statistical considerations of repeated measurements on individual animals

If the project succeeds responses will be analyzed identically from study to study, i.e. the statistical method will be identical for the same response independent of study. At the same time, statistical methods will be established to spot abnormalities (outliers) which could indicate some (important) adverse biological response.

5.2.2 TOXSASIS

An off spin of the project is an expert system to handle, analyze and report all data. The system is called "Novo Nordisk TOXicology & SAfety pharmacology data handling, Statistical analysis & study reporting Information System" (TOXSASIS).

The aim of TOXSASIS is an artifact that is able to migrate and load data from toxicity and safety pharmacological studies into a standard database where data are handled according to regulatory requirements in a way that secure data integrity. The system support data browsing, reporting and extraction to other applications. By automatic and on basis of the data structure it performs standardized statistical analyses and produces standardized reports.

The structure of the system is shown in figure 2. The system is divided in three main parts; a data handling module, a catalog of standardized statistical analysis macro's and a part that produces standardized study reports. What makes it an expert system is, that after loading data the results from the correct statistical analysis is summarized in a standard report. Hence, it is the structure of the data that determines the statistical analysis and the statistical analysis that determines the resulting tables and study reports.

The system has been developed by an innovative process. It started as a problem solving system but because the developing of TOXSASIS created new problems and thereby actively developed new knowledge to solve the problems it can be seen as an innovative development process. The knowledge was gained in close cooperation with the other actors participating in the development process (see section 7.1). Hence, we can refer to the development process as an organizational knowledge creation (see Nonaka [11]).

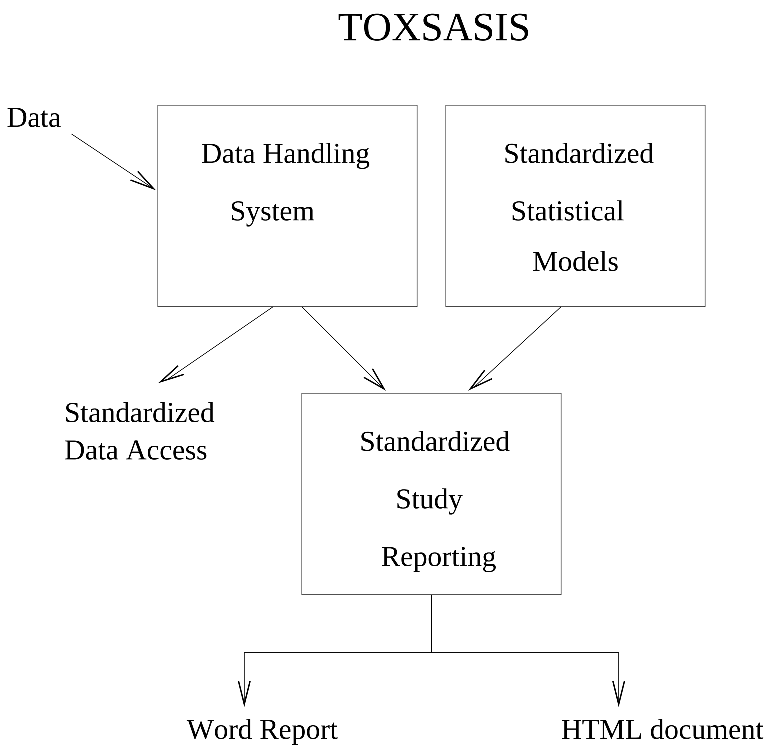

Figure 2: The flow diagram for the expert system, TOXSASIS.

5.2.3 Closening the project

An important milestone for the project is, that the methods developed become a standard within Novo Nordisk A/S. To reach that, we need first of all the authorities (in all the countries where we want to marketing our products) approval of the new method. Therefore we have to inform and discuss the possible methods through the developing phase with the authorities, because we need there input and approval of the assumptions we make. Furthermore we need the acceptance from the contract laboratories, that are going to used the new methods. To get that we again have to discuss our proposals. Both the authorities and contract laboratories get in contact with other pharmaceutical companies who are analyzing pre-clinical studies, and can thereby influence their way of analyzing data. In that way we may end up with a global standard for analyzing pre-clinical studies but even if we do not get that far our project might have started the discussion. The network will be further discussed in section 7.1 and 7.2.

Within the budget of the project there are resources for participating in conferences and visiting contract laboratories and other relevant persons. Another way of initiating the discussion is by writing articles which is also a part of the project. Through the project a “Road Show” has been developed. The “Road Show” consist of a PowerPoint presentation and interactively demonstrations of the database, the HTML presentations and other application modules.

6 The Ph.D. project in relation to the vision and effectiveness of the company

If the vision of Novo Nordisk A/S is evaluated as a strategy for both the shape of the portfolio of products and the structure of the portfolio of technologies [2] then the Ph.D. project is initiated in spirit of the company vision. Novo Nordisk A/S could in fact just have waited for some one else to set the standard for analyzing the toxicity and safety pharmacological studies in a consistent way, but in spirit of the company's vision they wanted to be the "best in the business" and "set the highest standards in everything they do". The Ph.D. project proves that the company is willing to pay what it costs to fulfill the vision of the company.

Besides fulfilling the company vision the Ph.D. project will hopefully optimize the operational effectiveness of the drug development process.

By standardizing the statistical analysis of the toxicity and safety pharmacological studies the following will be obtained;

- Faster statistical analysis and thereby decrease of the time span between end of animal experiments and start of phase I studies with volunteers.
- Reduce the statistical re-analysis and thereby time consumption, caused by problems with registration authorities not accepting the methods used.

By these means Novo Nordisk A/S will achieve increased competitiveness compared to its rivals, and because Novo Nordisk A/S will be first with a complete method to do the statistical analysis the company will be able to lead the development and thereby stay in front.

By improving the existing statistical models for the different toxicity and safety pharmacological studies and evolve new correct methods the company will obtain;

- More helpful results from models that are easy to understand and on a scale that fits the experimental results analyzed.
- Information to design studies with the right power so that decisions to select the best compound is helped.
- Ensure the right interpretation of the results from the studies.

In this way the new developed methods will also help to increase the operational effectiveness because the existing activities may be performed better (scientificly correct, more informative and precise) than before and better than the rivals.

7 The process of research and development

In this section the discovery and development of a new technology within Novo Nordisk A/S will be analyzed in a socio economic perspective.

The project phases which a new product is going through are shown in section 3, see figure 1. One objective of the Ph.D. project is to increase the effectiveness of the developing process and thereby indirectly render the selection process of a new product more effective.

First the discovery and development will be analyzed by a actor-network model for instance described by Callon [1] and the pull-push mechanisms described by Dosi [3] will be associated with the development process. Afterwards it will be described by a socio-cognitive model suggested by Garud and Rappa [5]. Finally, it will be explained how the innovative development process of the consistent statistical methods can have the effect that the methods become standard methods.

7.1 The actors network

The development of a new drug is a combination of a lot of different interests which are not steady throughout the developing phases. This can be described by an actor-network model [1], see figure 3. The actors in the project interesting in developing and marketing a new drug are; marketing, registration, quality assurance, medical writers, drug safety and statistical departments. All these partners work together to reach the final goal; launching a new product. Actors from the outer world interesting in the new product are; patients, doctors, other pharmaceutical companies and the authorities of health.

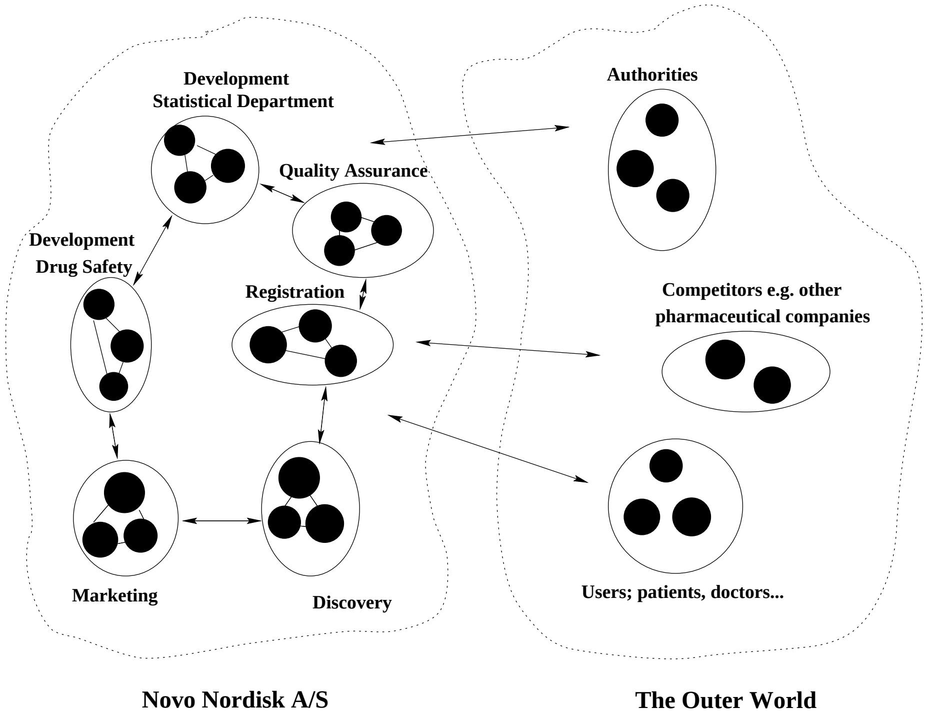

Figure 3: The actors involved in the development of a new drug.

In the same way the development of new methods and models for standardized toxicity and safety pharmacological studies can be described by an actor-network model [1], see figure 4. This model is a sub-model incorporated in the first one (model figure 3). Of course some of the actors are the same, especially those from the outside world.

The interactions that create the development process between the Ph.D. project group and the outside world (see figure 4) will be described in some details in the following.

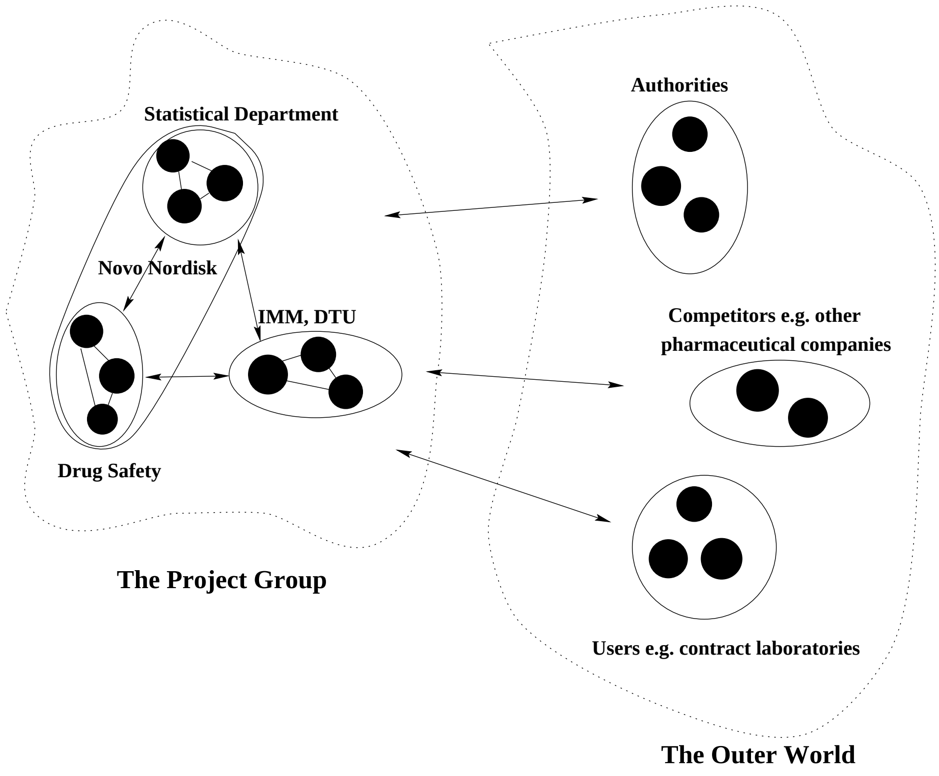

Figure 4: The actors involved in the Ph.D. project.

The Ph.D. project involves partners from the following institutions;

Department of Mathematical Modelling, DTU
The department at DTU is interested in the contact to the industry because of the inspiration for new research and teaching areas.

Novo Nordisk A/S
Drug Safety wants a complete system that can assist them in evaluating the results from the experiments and that is not doubted by the authorities.

Statistical Department at Novo Nordisk A/S wish to produce a system that is scientificly correct and makes Drug Safety capable of analyzing there studies by them self.

Actors from the outer world which may have interest in influencing the development process could be;

Authorities
The duty of the The Ministry of Health and Welfare is to secure the development process in a way that results in the best product for the users, here patients and doctors.

Competitors
The most serious insulin competitor of Novo Nordisk A/S is the American pharmaceutical company, Eli Lilly. Often the two companies are developing drugs with similar medical properties at the same time because both companies have discovered the same needs of the patients. Of course Lilly will do what is possible to delay the launching of a new technology from Novo Nordisk A/S. On the other hand, if Novo is developing something, like statistical methods which will be available for all pharmaceutical companies, they may not be interested in delaying the project because they them self can benefit from it.

Users
The patients want a drug that can cure diseases or simply make their life easier, but the drug is not allowed to have any adverse events and of course

the patients want it as fast as possible. Therefore, the users are interested in a new technology that can decrease the time used to develop a new drug.

The contract laboratories are the direct users of the new technology because it is them who will be asked by Novo Nordisk A/S to analyze the results by the new developed methods. They are interested in a technology which they can use also on experiments ordered by other pharmaceutical companies because it will make their work easier and simpler. This is why in fact the contract laboratories could be interested in participating in the developing of the new standard technology them self.

As shown, the different actors have different reasons for participating in the actor-network. It is the combination of the different reasons that forms the innovative development process. This can also be viewed in a pull-push theory e.g. described by Dosi [3] because some of the actors in the network have an inhibited influence on the process whereas other have an encouraging effect. Dosi [3] mentions the "demand-pull" and the "technology-push" as parameters that influence the development process.

It is the needs of the patients that pull the development of a new drug. They demand a treatment of their special disease which pull the process. On the other hand the company wants to use its technology and benefit from it, so here we can talk about a "technology-push". Other actors in the network acts as a guidance system. The authorities and doctors try to help, guide and provide a secure development for the benefit of the public.

7.2 A Socio-Cognitive model for the development process

In this subsection the development process will be examined as a social and cognitive process. A Socio-Cognitive model defined by Garud and Rappa [5] will be introduced and fitted to the development process of new technology knowledge within Novo Nordisk A/S.

Cognition is defined as; *the activity of knowing: the acquisition, organisation, and use of knowledge* [5] or said in other words "the action or process of acquiring knowledge and understanding through thought, experience or the senses".

The Socio-Cognitive model rests on three basic definitions of technology. These are: technology as;

- Beliefs: Technology success factors.
- Artifacts: Form and function.
- Evaluation routines: Testing standards and equipment.

A Socio-Cognitive model for the development in relation to the Ph.D. project is shown in figure 5.

Here the *belief* which is the fundamental of the development process is the idea that it is possible to standardize the statistical analysis of toxicity and safety pharmacological studies. The belief causes the models and methods to be verified on historical data. This is what the model calls *evaluation routines*. The belief also results in an *artifact* namely a SAS program that can perform the analysis (TOXSASIS).

The *evaluation routines* can therefore be expressed as; the verification of the methods and models developed. In order to verify the models a database (a part of TOXSASIS) with a lot of data from old toxicity studies has been developed. This is a very positive side-effect of the project because the database and TOXSASIS is a tool that the Drug Safety Department can use in the future. The verification of the models and the programs developed legitimize the *artifact*, here the SAS programs and TOXSASIS. The verification will also shape the *beliefs* over the developing period, because some of the ways in which the standardization was thought might be changed during the verification of the methods.

Again, the *artifact*, here the SAS programs, dictate standards for the evaluation routines because it restrains the possibilities for testing historical data.

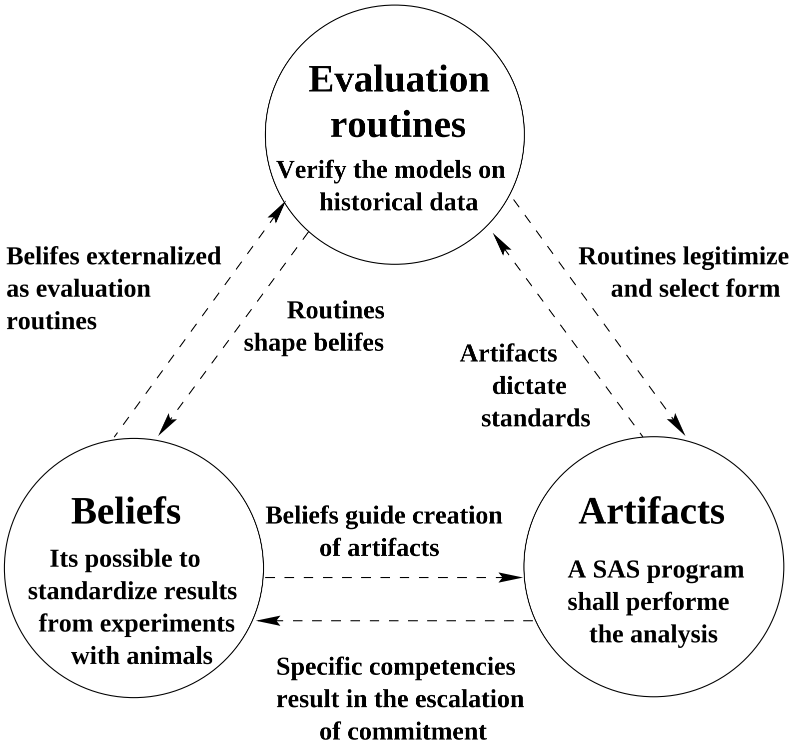

Figure 5: A Socio-Cognitive model for discovery and developing statistical methods and models at Novo Nordisk A/S. [5]

This is due to the fact, that Novo Nordisk A/S only wants to use SAS and no other statistical analysis tools because SAS is accepted by all authorities worldwide. In the same way the artifact affects the *beliefs* because again SAS could set some limits for the statistical methods that would reduce the possibilities of standardizing the statistical analyses.

8 Implementing a standard method

The standardization method have been developed by an innovative process. Hence, it has developed the organisation within Novo Nordisk because the different department involved in the project have learned by the development process [9]. As the members of the statistical group learned more about the toxicity studies it enabled them to build more correct models for data from the studies. Furthermore the cooperation made the design of the TOXSASIS artifact more suitable for the Drug Safety Department and by the cooperation the Drug Safety department has learned more about statistics and realized the need of statistical assistance.

The actors in the network influence the large possibilities of way of standardizing the statistical methods used. After considering all the actors special needs and recommendations the large variety of possibilities of standardization methods decreases to the final one, which then is a compromise of as many as the actors recommendations as possible. This elimination process is also described by Pinch and Bijker [13]. If the final compromise is accepted by all actors the method has the possibility of becoming an accepted standard method and not just the best method.

The "Road Show" described in section 5.2.3 has been presented for different departments and groups within the company and for some actors outside the company. To give a complete presentation of TOXSASIS is an easy way of presenting the concepts of standardization and proofing that it is possible to implement the methods. Showing an implementation of the theory is an important step on the way to agree about a standard method.

9 Conclusion

The Ph.D. project is a product of the network between different departments at Novo Nordisk A/S and the Department of Mathematical Modelling at DTU. The beliefs of the projects are based on the idea of standardizing the statistical analysis of toxicity and safety pharmacological studies. The goal for the company is to achieve an optimized effectiveness in the developing process of new products.

Some positive side-effects of the collaborative ventures have been established. A database with a lot of historical data and a data-handling system (TOXSASIS) has been developed and is almost ready for use. Besides the project has resulted in a smaller master's thesis project. The master thesis was also a joint venture between IMM and Novo Nordisk A/S, where Novo supplied the data and IMM provided the supervision. Furthermore the innovative development process has resulted in a gain of knowledge within the organisation of the company.

The company's hope for the Ph.D. project is that the results will set standards worldwide for the analysis of toxicity and safety pharmacological studies in a way that satisfy the authorities and thereby decrease the time for reviewing the registration files. The project has opened the possibilities for this standardization process by providing an almost complete software system to store, analyze and report data. Furthermore articles and oral presentations have been given providing the scientificly proofs for the methods.

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