Supporting drug development projects

Finding the requirements for an information management system
I would like to thank my parents and my brother for their support and assistance during the writing of this report, as well as Job Honig for his guidance and insight during the whole project.
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Summary

The development of drugs is a complex, long and expensive process. Kinesis Pharma is a company that helps drug developers by supporting project management and analysis needs of the developer. In their continuing effort to support their customers better, Kinesis is interested in researching the possibilities of using support software as a management and presentation tool. Current tools are lacking in support for drug strategy design, managing the changes during the development and communicating critical information to project participants.

Taking these issues into account, this has lead to the research question “Can the project methodology of Kinesis Pharma be supported by a tool that will help guard project strategy, project viability and information quality?”

To determine if it is possible to support the development of drugs in general and the methodology of Kinesis in particular, both are analyzed. On the supply side, an analysis of what support information technology can offer is done to determine if there is a match between the need and possible support.

Development of drugs is done on a project base consisting of actions performed to increase the knowledge of the active substance in a drug product, called compound. Actions can be studies where effects are measured, and analyses where measured results (“data”) are transformed into information useful for making decisions (“information”).

Due to the nature of the development it is set in a network environment, which affects the way information is gathered and made available. Complexity, financial demands and regulatory influences are all causes to include other organizations in the development.

The actors in the network have different levels of influence on the project. The researching organization sets a strategy, on which the actors assert their influence, ranging from the project strategy to a single study design.

Drug development is heavily regulated by scientific rules and legal regulations. These rules set a specific order to development projects, requiring information to be gathered in a specific order. The rules state that to gain this information, studies have to be performed to a specific standard of quality, as well as having the resulting reports and documents presented in legally compliant formats. Boundaries are set by time limits on the development due to patent time or competition, influencing the design and organization of the actions.

The rules influencing the drug development have created a project template that is compulsory for every project. This phased system is unique to drug development that alters the project’s structure. It divides s project into phases and gives each of these phases a specific goal.

The success of a project can be defined by developing a drug as long as it is a potential success. The goal distinguishes two types of success, the success of the project and the success of the compound.
These are considered separate as the success of one type does not affect the success of the other, and both need to be done successfully for the development of the drug.

The categories encountered when defining the success of the project are used to manage a project. When running a project, a distinction is made between managing and steering. Managing concerns the running of the project based on the project success factors, keeping track of time, budget and execution. Steering is done based on compound success information. Steering uses the current compound information to define and organize the required actions that need to be performed to gain all necessary compound information. Both steering and managing change the project often during the run. Due to the high uncertainty it is needed to track these changes to verify future and past decisions. Decisions are made by the project team, in which different members have different levels of decision power and information needs.

The main support should consist of information and decision tracking. The information’s unique structure and the decision complexity require a specifically created system, as there is currently no support available for this. The changes made during projects require an a history overview of the project, which has to enable the user to check the decisions against current knowledge. Support should provide network functionality, to grant access to information at different locations and times, while making the distinction between different users. The template used for drug development should support the phases and the goals set, as well as guide the different types of information that are used in the projects.

Drug development projects were researched on content and management. The projects information and decision making settings are very structured, which allows them to be modeled. This is the basis for support, which can be created if a developer takes the unique aspects of the industry into account. While it will take effort to create and maintain such a system, such a system will be able to support the Kinesis methodology of drug development and will solve the issues found in current support software.
1 Introduction to the Master Thesis

This paper is written as part of the master thesis project of Maarten Schuit at the Technical University Delft for the faculty Systems Engineering, Policy Analysis and Management (SEPAM).

The setting of the research is in the pharmaceutical research and medicine development industry, where Kinesis Pharma is a world leading consultancy firm in drug development. Kinesis supports companies performing drug research with industry expertise, project management and data analysis.

The introduction chapter will outline the five following topics: Background (of drug development), Issue formation based on internship at Kinesis Pharma, Research goals set on findings at Kinesis Pharma, Research Methodology, Scope: defining the boundaries of the research.

1.1 Background

The development of new medicines has been and will continue to be a very important factor for human welfare. Healthcare of the 21st century could not have become what it is now without the creation of modern medicines and drugs that counter an ever increasing number of diseases, viruses and other clinical conditions. Progress in other realms of science has opened up many new opportunities of developing medicines. Using advanced methods of creating new drugs has significantly increased its potential number. These additional potential drugs will lead to new medicines for clinical conditions that have no treatments and the improvement of currently available treatments. One part of the pharmaceutical industry is solely dedicated to the development of new medicines and drugs. It is their goal to create new counters against ailments and find cures to diseases in order to make quality of life better for everyone.

Creating a new drug is a long term, highly specialized, costly and risky endeavor. The process of finding a drug compound that might be used as a medicine requires in depth knowledge of field of chemistry, pharmacy and biology. This is only the first step of creating a new medicine. The discovery should be followed by a thorough investigation of all the drugs’ effects. The development of a drug is a turbulent series of research studies, which require more expertise in additional fields of science. During its development the compound must be tested on all of its effects, the good and, especially, the bad. To test all these aspects can take many years. Extensive testing is done under strict regulations in order to guarantee safety for all involved. In many cases, a project approach is used, with its own company or own team that is dedicated to developing a compound. The average duration of development for a successful drug is around eight to twelve years. The estimation of the costs to develop a new drug is around one billion Euros. Financial risk stems from the fact that not all drug development will be successful. The current rate of success is about one in five hundred [Evens, 2007]. That is, for every five hundred compounds that seem viable to become a medicine, on average, only one will succeed. Compounds can fail for many reasons, it didn’t perform well enough, there were unacceptable side effects, it would be too expensive to manufacture it or the patient group would be too small to make it economically viable. A failed compound in most cases means a
complete loss of investments. Success allows the developer to market the drug and recuperate the made investments, though the time for that is limited. Like most patents, patents on drugs have a limited time span: about twenty years. Once a patent has expired, other drug producers are allowed to copy the drug, usually taking away a large part of the sales of the original company. About half of the patent time will be spent developing the drug, which sets high requirements to profitability.

Getting a compound to be allowed on the market is a complex task as well. Not only does it require the technical knowhow of the chemical and pharmaceutical sciences mentioned above, many fields of business have to be included for the compound to be a success. A critical field the compound should comply to is set by regulatory control, governmental organizations that guard public safety. Other fields include, but are not limited to international legal research, marketing, financing and manufacturing. The development requires the input of so many fields that it is impossible to have one man or even one company have all necessary skills alone [Evens, 2007]. Many different organizations offer opportunities to perform specialized research on these fields, running trials at their facilities, analyzing local regulatory requirements or allowing to perform market and finance studies. To this effect the development of drug compounds creates a multi actor environment and should be considered a network endeavor. The researching organization has to manage the various organizations that are included in the development.

1.2 Issue formulation

Kinesis Pharma has years of experience in the pharmaceutical industry. The company has identified a lack of support for determining and managing project strategies. This includes tools to measure and convey the success of a project and decision support systems that will identify, track and record the many changes made during a project. Issues found at Kinesis can be fit in three categories:

- Measuring the results of a project
- Goal and strategy management
- Information sharing between participants.

In order to reduce the development risks as much as possible, a close watch is kept on the performance of the compound and the project during development. This is not an easy task, for not only are the issues complex and highly technical, it can also be difficult to measure the performance of a compound, predict whether it will be “good enough” to reach the end of the development cycle. During the development, internal developments and external influences evolve, changing the project settings and altering issues. Even if these changes are detected, it is not immediately clear what to do with this information. Expertise and experience are required to stay on the optimal development path.

Defining the success of a project is a complex task by itself. The success of a project is based on two factors, the actual results and the required results [Beroggi, 1999]. The first factor is difficult to predict and can only be filled in by research. Setting criteria for the required results is a fine art of expectancy management and testing to regulatory requirements and current competitors. These factors make it very difficult to set hard criteria for a compound to measure against. Criteria differ
and change during each project, which causes uncertainty about the effectiveness of project success measurements. Methods and assumptions vary between researchers and if the approach is not set clearly to measure results, these criteria will be interpreted differently. How to measure results is one aspect that needs to be agreed upon by the project team. Additionally the criteria need to be clearly established and motivated. In projects where many of the parameters will change during its run, criteria may need adjustment to accommodate these changes. If there is no clear link between the influencing parameters and the affected criteria, a project’s goals may become outdated and wrong.

Goal erosion [Bots, 2000] is the second danger when objectives are adjusted and this is not managed well. Goal erosion is the alteration of goals, usually caused when outcomes are only slightly different from expected results. Instead of taking a firm stand and holding on to criteria set, the project team accepts results just below the requirements, as they are so close to the original goals. The criteria and the goals are adjusted. Goal adjustment is not a negative effect per se: it is used during projects when new insights are integrated into the project and can keep a project realistic, or to revive a compound for a different clinical condition. However, with the costs of development being as high as they are, these adjustments can lead to a situation where a compound is researched beyond the point where it should have been recognized as unviable. While goal changes are unavoidable [Groen, 2007], the viability of the project should always be kept in mind. One of the problems is the difficulty to keep track of criteria and outcomes, as most of the existing project methodology is focused on the results of actions and not on goal and criteria changes during the project. In projects with frequent criteria and goal changes, decisions made in the past are made based on old goals [Krishnamurthy, 2007]. In order to understand these decisions, one must know the goals of earlier date. Currently there is no project management tool that can handle evolving goals.

A closely related topic, but on a slightly different level, is the difficulty of strategy management. The strategy that guides the development of the compound is the result of different factors. Sponsor preference, industry and legal constraints, budget and time issues are just a few of these factors. The strategy sets preference and optimization rules for alternatives available during a project. The development plan at the start of a project is based on the strategy formulated at that time. During a project, information changes, external effects exert their influence on the project and a project team may change. These and other effects can influence the development strategy. Due to the long term and large intervals between events during development projects [IPA, 2006] in this industry, it is difficult to maintain a clear overview of the optimal strategy if these factors are not defined and updated. Without appropriate strategy maintenance, it is easy for a project to run out of control. However, no known support system is equipped to handle change management with the required flexibility and strategy management that would seem to be necessary here.

Last of the issues found by Kinesis Pharma was the difficulty of presenting a clear project status to project participants and external parties? Even though the majority of the decisions in the development is made by the project team this team is usually not, it will be required to report their progress to higher levels. Even if a company is set up specifically for the development of a compound, it is very likely it will need to report to some form of higher ranking board, i.e. a financial backer or mother company. Most often higher ranks will make the budget decisions on which the development project depends.
Presenting results may color the information [de Bruijn, 1999], even if that is unintended by the project team. This will influence the decision maker to adopt the point of view of the information provider. For decision makers sufficient, uncolored knowledge on the status of the compound, the chance of success and the overall project status is required. Presenting information in this way is not easy in pharmaceutical projects, where the status is not only dependent on compliance to above mentioned subjective criteria and strategy. Data to test to this compliance is generated by many different parties, potentially adding more subjective influences to the information. The large amount of information available further complicates the presentation of the actual status of the project. In many cases, mostly periodic sessions are required to bring decision makers up to date on the events of the project. While this solves the problem of information supply, it requires much preparation. Kinesis currently estimates the time requirements for bringing all participants up to speed about two weeks [Kinesis, 2007/2008] per “big” decision. With each project having at least eight of these decisions [Kinesis, 2007/2008], this is an average delay of two months per project. This might not seem much in a ten year project, but consider a drug with an annual revenue of 100 million Euros¹ and one can see this delay can reduce the revenues of a company by sixteen million Euros. Kinesis has stated they would like to have a system that will allow participants to gain clear information on the project status without incurring these delays.

Systems Engineering & Policy management at the Delft University of Technology focuses on solving highly technical problems by applying technological and managerial innovations. An important part of creating a solution is finding the exact problem. After preliminary analysis, the three fields of issues were divided into eight separate topics concerning the lack of support for drug development projects:

- The design of a drug development strategy
- Management of a project development strategy during its run
- Show the interaction between study results and the project planning
- Generating an overview of project mission critical information
- Supply uniform information to all participants at the project
- Being able to present insight in the status of a project at a moments notice
- Being able to guarantee decisions are made by the right person for the right reasons
- Being able to recheck options for “failed” compounds and check for additional options for current ones

¹ 100 million Euros is the mean of drug revenues in the first year on the market. However, one could argue that this extra revenue would be applicable at the end of the patent period, in which case the drug would have become better known and better sold. [Priti, 2007]
Kinesis Pharma operates as a consultant for companies that carry out drug research worldwide and has been active for ten years in this field. Kinesis Pharma has experienced that no real support tools for high level project management exist for the pharmaceutical industry. At this early stage, it can be stated that there is a considerable difference between many of the theoretical approaches and the way projects - not just Kinesis’ projects - are actually run in this industry. This is caused by the unique nature of the industry, which may explain the lack of support for such projects. Kinesis feels that it can provide better services to their customers with a tool which will manage project strategy, decision making support and project planning changes. The wish to have such a tool has resulted in the request to research the possibilities to develop such a tool.

### 1.3 Research goals

The issues identified by Kinesis were described above. After identifying the issues, the next step is to formulate an approach to find solutions. In order to do so, a number of questions is formulated to solve these issues. These questions are the research questions that must be answered to find a solution to their main issue:

“Can the project methodology of Kinesis Pharma be supported by a tool that will help guard project strategy, project viability and information quality?”

To find an answer to this question, research is divided into two stages. The first is qualitative research of the practice of development management. The second is the research of the possibilities to add support to development management. These two stages each have their own sub-questions:

1. How does Kinesis Pharma approach drug development?
   a. What are the general settings for projects of this type?
   b. How are projects run and how are evaluations done?

2. Can the Kinesis Pharma approach be supported by an information system?
   a. What are the requirements the industry, the projects and Kinesis might demand from such a system?
   b. What functionality can such an information system provide?
   c. Is there a match between the required functionality and the functionality that is possible to be provided?
1.4 Research methodology

A number of fields of research are identified in the description above. First the project management perspective in these development projects is apparent. Secondly, issues in the area of network management can be seen as actor relations and information sharing. Last, and most important, is the necessity to analyze the needs and to create the design of the tool. In this research area the science of systems engineering is applied. In this thesis the systems engineering methodology is used as a general approach, the additional fields of science needed, such as project management, information analysis and software design, will be introduced at the time of their application. The three steps of developing a system according to systems engineering are Definition, Development and Deployment.

Definition
In the definition stage all the relevant issues and their causes are defined. It will also map the industry and its different contributing factors, such as business environment, network surroundings and information management. This will show the needs and possible points of interaction with the environment. This definition phase was executed during the internship at the location of Kinesis, where passive drug development project observation, archived studies and interviews with their project teams has been the source of information. Chapter two and three will present the findings of the definition phase.

Literature research provides information on project management support systems, of which the theoretical component will be used to create the framework of the requirements. It can be evaluated by comparing the component to project support tools in different project management environments.

Development
In the development phase the environment specifics in the current situation are translated into the creation of functional requirements. Essentially, the support system has to satisfy the user’s needs. Functional requirements are created by the combination of the definition stage and the application of systems design theory. From the information gained in the definition phase, the structure of the project strategy and the information requirements will be found. This general structure with its requirements then can be compared to available support. In case of lacking support, Systems engineering and decision modeling form the theoretical basis to identify and design the functional requirements. These steps will be shown in chapter five.

Deployment
The last stage is deployment. This is the stage where systems can be introduced, used and evaluated in the organization. The duration of the master thesis project is not long enough to cover the evaluation of a system designed to manage a complete development project. To compensate for this, the evaluation is done on functional design and mock-up review, which can be found in chapter five.
1.5 Scope

The drug development industry is a very interesting industry with many challenges. This thesis will be focused on the creation of a tool to support drug development strategy. Drug development is a large field; so large that to create a support tool of which the whole development can benefit would take more time than is available for a thesis. Research focus is put on the support of the development strategy, as this is where the main issues were found by Kinesis. This means that some aspects of drug development that have little influence on the strategy will not be taken into account, even though they are part of the overall development.

The thesis will explain the structure of drug development projects, without trying to lecture on the ins and outs of drug development. Where knowledge of content is needed for understanding the business, required information to solve the problem will be given. Most of the content will therefore be identified and analyzed to a level where its mechanisms are known, but more detailed specifics will not add relevant information to a support tool if experts will use it.

As the tool is meant to support the strategy of a project, its focus should lay there. This differs from project management systems that manage the operational level. These systems already exist and are often well suited to manage that aspect of drug development projects. Most of the operational level information and results will therefore be considered outside the scope of this research. However, in order to track the strategy, information on results and processes will be needed, so a method to select and track strategic information must be found. This will occasionally require the tracking of lower than strategic information, but this is not a main goal. The tracking of these results is a means, not an end.

The majority of the strategic decisions are made at the start of the project. At a later stage alterations and fine tuning of the project may be introduced, but most of the important decisions are made in the first phases of development. This thesis will mainly focus on the earliest phases of development to deal with these most important decisions.

Two aspects gaining importance later in the development are marketing and legal affairs. Though these are essential for the successful economical exploitation of the drug, they often have little influence on the development route, especially at the early stages. With exception of the comparison to competitor products and the regulatory control during the development, these two fields will be outside the scope of the thesis.

Many large companies use portfolio management systems to help divide resources between their projects. The scope of this thesis is just below that level, it focuses at the individual project. The thesis should provide insight in the running of one project and all its critical factors. It is not supposed to be a tool to manage Clinical Research Organization’s project interactions. While the portfolio management systems should be able to use the information gathered here as a perfect source, this is currently not the goal.
2 The pharmaceutical industry

In this chapter, the pharmaceutical industry is analyzed to define what effects the industry environment has on drug development projects. This will start with a general analysis of the industry. The different organizations encountered during drug development are analyzed in section 2.1 as well as the effect they have on a development project. Factors and influences affecting the development projects are analyzed in section 2.2 to determine how they influence the development. In section 2.3 the “standard” template for drug development projects is introduced.

Drugs are defined as substances that alter normal bodily functions. Medicines are a special category of drugs with the specific application of maintaining and restoring human health. In the pharmaceutical industry, creating new medicines is therefore more often referred to as drug development rather than medicines development, as many of the developed compounds (which is the active substance in a drug) fit within a broader scope than maintaining human health. There is a large variety of drugs, some to improve health by replenishing a natural deficit in the human body or treating a disease, some improve quality of life by reducing pain or adverse effects. Drugs in this sense are not to be confused with the “recreational drugs”, all medicinal drugs are legal to use if properly prescribed by a doctor or MD. The legal drug market is huge, with a global size of around 400 billion dollars in sales [IMS Health, 2008]. This is the total amount of money spent on medications, on drugs that are still patented or off-patent. Part of this revenue is used for the development of new drugs, which has an estimated global annual research budget of 32 billion [AR, 2006].

The research of drugs is mainly located in the US, Europe and Australia, though lately Asia has been growing as a provider of research facilities as well. Nationality for research results is not a very important factor, though in each region or country, different requirements for studies, results and safety may be in effect.

2.1 Analysis of drug development actor network

The development of new drugs is done by a relative small number of companies. An estimated twenty thousand legal companies engage in drug research, most of them small companies with only a single compound in development. Only a score of large companies have the capacity to develop multiple drugs at the same time and manage all aspects of the development. Smaller companies are dependent on external organizations performing the tasks they cannot. This has led to six types of organizations, each has specific areas of expertise [Evens, 2007]. A full analysis of these actors can be seen in Appendix A: Analysis of drug development actor network, which is summarized in the list below:

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2 A global estimate of 20,000 companies do drug research, mainly in the US, Europe and Australia. As a comparison, India alone has more than 50,000 companies in drug retail. [E.M.E.A., 2005]
• **Research Organizations (RO)**

This is the organization that has a drug to develop and has created a development project to do so.

• **Venture Capitalist companies (VC)**

Venture Capitalists invest in drug development projects and provide funding to perform research. In return, the VC will receive a return on the investment once the drug is developed.

• **Clinical Research Organizations (CRO)**

Clinical research organizations are organizations that perform most of the actual research. For this these organizations have specialized laboratories and test centers that enable them to do the research.

• **Specialty Service Companies (SSC)**

Companies of this type provide analysis and reporting services that an RO cannot perform due to the required expertise.

• **Communication and Market Research companies**

These companies help to sell the drug once it marketed and help analyze the market need for drugs.

• **Law and Regulations Organizations.**

Drug research is regulated by these organizations, they set safety requirements for all the performed actions and drugs under development.

The large companies have all these organizations departmentalized within their organization, while small companies are mostly classified as research companies. Typically such companies use venture capitalists companies to fund their research and use external clinical research organizations to carry out much of the actual research. Kinesis falls within the classification of specialty service company. Specialty service organizations may provide statistical analysis, formal reports, study and trial management or any other services that are generally needed but don’t require their own department in a small organization. During the development, marketing and patent submissions have to be done in order to guarantee returns on investment, which might be outsourced as well.

The sources and reasons of searching for new compounds can vary significantly. Discoveries have been made in universities and research laboratories or are based on traditional medicine. Some come from theoretical research, targeted clinical research, molecular engineering, re-examining compounds that failed for their original clinical conditions or the occasional dumb luck. Some perform this research to find cures for illnesses; others do it for more mundane rewards.
Analysis of network influences

In this section the distinction between different actors is analyzed on how the various actors set requirements that affect the drug development project. In table 2.1, an inventory of the actors and their influences is made.

<table>
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<th>Actor</th>
<th>Dedication</th>
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<td>Yes</td>
<td>Yes</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Venture Capitalists (VC)</td>
<td>Yes</td>
<td>Variable</td>
<td>Yes</td>
<td>Variable</td>
<td>Low</td>
</tr>
<tr>
<td>Clinical Research Organizations (CRO)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Specialty Service Companies (SSC)</td>
<td>No</td>
<td>Variable</td>
<td>No</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Communication and Market Research</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Law and regulatory</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Low</td>
<td>Variable</td>
</tr>
<tr>
<td>Kinesis³</td>
<td>Variable</td>
<td>Yes</td>
<td>No</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

Table 2.1: Actors and their influence on development projects

The meaning of the meaning of the columns is as follows:

**Dedication** shows that the actor has an active interest in seeing the project become a success. In a normal project setup, the only dedicated actor other than the RO is the VC, who likes to stay informed on his investment. Kinesis will be a dedicated actor in its normal role of project management, in which case Kinesis needs to report its progress to the RO who is usually the link to the VC.

³ Kinesis is mentioned separately from the Specialty Service Companies, as their services are beyond the scope of a “normal” SSC. Kinesis in the table applies to Kinesis in the project management role. If Kinesis is hired to perform only duties that fit in the normal scope of the SSC, they should be considered as an SSC.
Decision power is the power to actively steer the project’s course. Theoretically, the RO is the only organization with decision power, though a VC can have this power as well, dependent on their agreement with the RO. Kinesis assumes decision power when they manage projects, though this is only for low level decisions; high level decisions will always be presented to and made by the RO.

Blocking power is the ability of an actor to delay or stop a project. The RO can stop a project at any time, which is done when the project does not meet its objectives. A VC has blocking power by withdrawing support (funding) from a project, which will temporary halt or in the worst case cancel it. Regulatory organizations can block and cancel a project when information needs are not met or when results do not match guidelines. This can either block the progress of a project until the required information is delivered, or cancel the project by refusing to continue testing on a specific compound.

Level of influence shows the influence of an actor on the development strategy. The RO has the highest influence of all actors and sets boundaries on budget, time and compound objectives. The VC has mainly financial power, which have a varying degree of influence. CRO’s influence the development at study level, by setting boundaries. Typical SSC influence a project in a similar way the CROs do. Regulatory organizations influence studies with national regulations, but do not interfere with the project directly. Kinesis uses its expertise to help steer the project and can advise on issues, which gives Kinesis a high amount of influence.

Information need shows how much information an actor needs to perform its task for the project. For an RO, the information need is high, as it needs as much information as possible to guide the project well. The VC has low information needs, he does not need to make decisions to control the project. VC’s often state they have a high information need, but this is strategic behavior to gain more control over the project. CRO’s and SSC’s do not require a lot of information, they just need their assignments. Regulatory offices have high information need, but only at specific periods during the project (see Appendix A for more information). Kinesis, if they manage the project require as much information as a RO running a project.

The table shows that different actors have different powers to influence the project. It is not only the power that differs per actor, but also the way this power takes form. As can be seen, the CRO and the marketing organizations have the same profile. However a CRO has the power to set the specifications for studies done at its location, while marketing provides additional information to set objectives to. This shows that different actors affect the project at different levels.

Also found was that actors influence other actors, sometimes directly, sometimes indirectly. These interactions are shown in Figure 2.1.
Each of the actors will assert his influence on other actors in the project. Each of these influences takes different forms as the method of interaction with the other actors is different.

Kinesis and the RO are grouped as one actor, the drug developer. Within this actor, they freely share information and goals, though there can be influences between the RO and Kinesis as well. This will be explained in section 3.2 where the project team is explained. The interactions the external network has are on the project have a very different scale from this, as is shown below.

The Regulatory control sets regulations to which a drug developer has to comply. For the RO, this means that the types of research or the order in which it is done is regulated by regulatory control. The regulations also affect a CRO in methods and the quality of research they are allowed to use. They will affect an SSC by setting requirements for the documents and analyses made at the SSC. Marketing research is regulated indirectly, these organizations check the regulations set for a drug to help set objectives.
A CRO can set research requirements to a drug developer, which is usually in the form of standard operation procedures or national regulations. Together with the RO, the CRO will come to an agreement how to do a study at their facility.

An SSC also sets requirements for an RO, but in this case this is done by setting analyses constraints, which are dependent on the expertise and experience of an SSC. The SSC influences and is influenced by a CRO in the way that by setting requirements for their analysis, they can change the study requirements the RO set to a CRO. The other way around is possible as well, a CRO’s specific operation procedure can set requirements to the analysis done at an SSC.

A VC mostly demands a return on investments, which translate in required results. A VC can go as far as demanding changes to be made to the project strategy.

**Different methods of communication**

The different actors communicate differently with the RO. These difference are significant, communications methods used for one type of actor are not applicable to any other actors.

A VC usually has little understanding of the drug development industry and is not interested in the pharmacological and chemistry information of the compound. Instead, they are more interested in end product performance, project success and drug viability.

CRO’s require detailed information on their specific tasks. This information can be supplied asynchronous, sending the research requirements to a CRO for their analysis. With this information, the CRO applies their own Standard Operating Procedures to the required research and sends a research protocol back. This gets verified by a project team specialist before it is accepted and the study can start.

SSC’s require detailed information for their required analysis and tasks. As the tasks for which SSC’s are required are highly specialized, the information these organizations need is very diverse but specific.

As will be shown in section 2.2, Regulatory affairs have their own requirements for communication, which are very different from any of the above mentioned types.
2.2 Aspects influencing drug development

Designing a drug development project is more complicated than just gathering the different organizations and assigning them to perform research.

The drug development process is influenced by many factors that influence the freedom with which projects can be designed. These influences affect the project in different ways, so in order to be able to guard the project, these influences and the manner with which they interact with the project must be understood. In this section, these factors are analyzed whether these influences and interactions can and should be supported.

This starts with a summary of the encountered influences, which will be followed by an analysis how these influences affect the projects. The influences can be divided into four categories, Rules and regulations, economic aspects, scientific aspects and influences due to completion. A complete description of these influences can be found in Appendix B: Influences and effects on the drug development.

Rules and regulations

The rules and regulations affect the drug development project heavily. Set by regulatory offices, these regulations often leave little room for negotiation. Regulations affect all aspects of the drug development project, including the way drugs are tested, how projects are organized and what information needs to be gathered. The regulations can be divided in the following categories:

- Safety requirements
  These set requirements for the safety of the compound, setting strict boundaries for the allowable adverse affects severity during testing and when presenting a compound to the market.

- Requirements on research sequence
  Many studies are not allowed to be run without prior knowledge of the potential effects encountered during those studies. This requires other studies to be done before the requested study may start.

- Regulations on research quality
  To ensure the research is done correctly, regulations have been set for research standards. These standards must be adhered to create information for official and final results.

- Documentation requirements
  Due to the highly specified and diverse research fields, official rules have been set for creating documentation to prevent miscommunication.

- Communication with regulatory organization requirements
  To ensure the regulatory organizations are kept up to date they require the RO to provide information on the compound and planned studies at specific moments of the project.
Economic aspects

Actions and studies add value to the project, while costing an investment of capital and time. These investments can differ significantly per action and study, so if other influences allow it, actions are optimized to a path to provide the most result while requiring the least investment.

Scientific aspects

The studies done during a project are affected by scientific dependencies and changing information need. Some studies cannot be performed without prior research, which can be needed to identify the specific research requirements for a study or identify the study types needed to continue the project.

Influences due to competition

Competition adds three important factors to a project, these are “time to market”, “project information secrecy” and “result requirements”:

• Time to market

Having a development project take as little time as possible is important as it will allow more time to gain a return on investment before the patent runs out. It is also important when there is development race between competitors going on, the first one on the market is perceived to have less trouble during development and is therefore perceived to be better.

• Security

Information on a compound is guarded. Not only can presenting information endanger the patenting process, it will enable competition to better control their compound development, endangering the potential success of one’s own compound.

• Result requirements

Regulatory affairs has set rules that if there are product available for the same clinical condition, new products must have distinctive properties, such as having less adverse effects or requiring less uses per day.
Analysis of factors influencing development projects

Requirements and regulations change the options the development team has to design their projects. These limitations affect the project design at different levels. The most basic level is the regulations affecting the information requirements, stating what aspects of the compound need to be known. This indirectly affects which studies need to be performed during a development project, which are needed to gather this information. The regulations also directly influence the actions needed during a project. This can be as simple as stating what actions need to be performed or in which order.

The actions that need to be performed are set by the information requirements. Research requirements set by scientific and economic factors affect how as well as in what order the actions should be performed. Dependent on the project, studies are required to focus on different aspects of the compound and have to be performed in a specific order. The project actions produce results, these results are used to gather information on the compound. For this, the results requirements must be met, which are not only measured by the quality of the research that was performed, but also on the results this generates for the compound. Finally, there is a feedback loop between the results and the research requirements. The information gained from the results is used to set future research requirements, which can be in the form of finding new compound research topics or in the form of setting requirements for the designs of actions. An overview of the effects and influences can be seen in figure 2.2:

Figure 2.2: Factors influencing development projects

The exact factors influencing a project are mainly determined by the compound being researched, targeted clinical condition and targeted population which makes every development project unique. Due to this uniqueness, it is impossible to create a standard list of actions needed in a project. It is possible to categorize actions into types, but which of these types of actions will be needed cannot be standardized. Even when an action of a specific type is used, each development project sets specific requirements to these actions, requiring the design of every action. If the development of a compound is to be supported, the support should be at a fundamental level, such as a way to model the influences and their effects and from this select which actions are applicable.
2.3 The drug development template

Projects for developing drugs have a distinctive set-up. This setup divides a project in phases that each have their own sub-goals and objectives. The phases are a result of regulations and requirements based on safety issues, limiting the kinds of research allowed in each phase. As a project moves into a next phase, additional types of studies are unlocked. It is a legal requirement to use a phased system; at the same time, it is a sensible way to organize a project, so there is little need for alternatives [Evens, 2007]. The current architecture of the phased system is the result of many years of international experience with drug research. Evolving safety regulations, economic requirements, scientific dependencies and participant actions have all had their influences on the industry and have shaped it into the current development template. This template provides a loose set-up for each development project, ensuring that no important factors are skipped or done before or after the point where they are (most) useful.

Within these templates, a lot of room for customization is necessary for each unique drug development. Using the unique aspects of the compound, studies and analysis are defined and planned according to strategy, resulting in the project plan. Any project plan (and strategy) should fit within the template, however. Analyzing this template will give insight in how projects look, which is important when creating support for guarding the development of a compound.

An overview of the drug development project template

The development of a drug is divided into seven phases to manage different aspects of the drug, such as safety or dose setting. Each phase has specific objectives, which need to be reached to go to the next phase. As phases progress, research is focused on different aspects of the drug, starting with safety requirements and progressing to effects and use requirements. An overview of the phases of drug development can be seen in figure 2.3. Each of the phases is presented below with their main goal. A more complete overview of the phases and their sub goals can be found in Appendix C: The phases of drug development.

![Figure 2.3: Phases of drug development projects](image-url)
Discovery phase
This is the phase in which a compound is identified, beneficial effects are found that are worth starting a development project for.

Non Clinical phase
In this phase, the basic safety is established, which is required to allow testing the drug on human test subjects.

Clinical Phase 1
A first test on healthy human volunteers used to find any unpredicted adverse effects.

Clinical phase 2a
The first tests to see if a compound is effective, this phase is used with a large variety in doses to determine the drug’s efficacy.

Clinical phase 2b
Using the information from phase 2a, this phase is used to determine the optimal dose for a drug.

Phase 3
In this phase, the nearly finalized drug is tested to find out if the drug is good enough to market.

Phase 4
In this phase, the drug has been marketed successfully and the feedback of users worldwide is used to improve the knowledge of the drug’s performance.

Analysis of the drug development template
The phases in drug development structure projects, which is both a benefit and a disadvantage for the drug developers. It makes it easier to design a development path, as clear rules are set to what actions are allowed at what time. At the same time, it creates more overhead, adding phase goals that may not be essential for the project to be measured.

For the creation of support, the phase system helps structure the actions, making them more easy to categorize and organize for presentation. As was found in section 2.2, standardization of action types is possible, concluding from section 2.3 the actions can be presented in a method that is familiar for the project team.

The phase goals are all focused on how the compound performs on specific aspects. These goals are presented in table 2.2, where the goals per phase are presented. In the same table, decisions made about the compound are identified as these are tied to the goals. More information on these decisions will be provided in section 3.3.2.
The additional goals require additional modeling just as they require additional tracking in the real life projects. In section 3.3.1 the method of modeling goals will be presented, phase goals can essentially be modeled using the same method, so this would require little additional support functionality.

<table>
<thead>
<tr>
<th>Phase name</th>
<th>Phase goal</th>
<th>Decisions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Discovery phase</strong></td>
<td>Finding the mechanism of action and strength of the effect</td>
<td></td>
</tr>
<tr>
<td><strong>Non clinical phase</strong></td>
<td>Best compound selection Non clinical Safety testing Formulation research</td>
<td>Select lead compound Select a formulation</td>
</tr>
<tr>
<td><strong>Clinical phase 1</strong></td>
<td>Safety testing in humans Formulation research</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical phase 2a</strong></td>
<td>Trial efficacy Dose ranging Formulation research Set clinical condition / indication</td>
<td>Set dose range Set a clinical condition</td>
</tr>
<tr>
<td><strong>Clinical phase 2b</strong></td>
<td>Setting the dose Set clinical condition / indication Efficacy testing</td>
<td>Set dose Set an indication (optional)</td>
</tr>
<tr>
<td><strong>Clinical phase 3 (Pivotal trials)</strong></td>
<td>Final Dosage Efficacy testing</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical phase 4</strong></td>
<td>Continued testing on the commercial product</td>
<td></td>
</tr>
</tbody>
</table>

Table 2.2 Phases, Goals and Compound decisions
3 The management of drug development projects

In this chapter the management and running of drug development projects will be analyzed. The need to know how information is used and managed will be the subject of section 3.1. In section 3.2 the decision makers are presented. Section 3.3 will focus on the mechanisms of decision making and the decision types a project team can expect.

3.1 Information in projects

Information is vital for a project. Not only is the goal to gain a certain level of compound information to show how the compound performs; information is also needed to gain insight in how the development of the compound is progressing. Information is a complex commodity, it changes through time and doing actions and will have unknown effects on the development project. As it is the only way to effectively steer a project by, an analysis of the information, the way it is used and gained is needed.

What is information

The first step is to establish what information actually is. In literature, a difference is made between data and information [Krisnamurthy, 2007]. Information is that part of the data that is actionable, which means data that can be put to use. In drug development projects, making this distinction is essential, as studies generate large amounts of data, most of which is not actionable.

The difference between data and information is in the interpretation of the data. A development project has different information needs at different times, depending on this, a selection of data is used, this selection is the information. Data is the original captured outcomes during an activity, a study in this case. To derive information from the data, it is not enough to select parts of the data, to be usable, the data has to be transformed by analysts. The transformed data is referred to in this field as meta data. An example of changing data into meta data is the transformation of tables into graphs: while the outcomes are not changed, the information value is increased, as it is easier to understand how the measured properties behave. Data transformation helps narrowing information down by adding presentation methods and observations to it.

Studies and the data they produce are static. This means that they will only present data based on the setting of the studies at the time of their start. It makes proper analysis of the data that a study will provide essential. Errors here, or changes later in the project will not change any of the data found and recorded in the study reports, they just render the study useless. It is a known issue that studies need to be redone because the resulting data cannot be transformed into information. The

---

4 This is incorrect use of the term meta-data, which is commonly used as data about data.
results do not provide any of the needed insights to continue the project. In such cases, studies need to be redone.

Transformed data files, just like raw data files, are static. Once transformed, no changes will be made to the files. If additional data is collected, it will be supplied as new documents and files so a topic may have multiple data sources if additional research was done. Decision makers therefore need multiple sources of information. Complicating matters more, the data is not always available simultaneously, which makes ensuring one has all the available data an issue in itself.

Data needed to build information can have multiple source actions, so the relationship between data and actions must be tracked. The degree of dependency varies between “need-to-know” and “nice-to-know”. This degree of information dependency is encountered in both decisions and designs. Some decisions cannot be made without prior studies, while other decisions can be made although the quality of the decision may be affected. The “need to know” information is the primary source for making a decision: without it, no decision can be made. The “nice to know” information is secondary information, used to gain more confidence in the decision. If secondary information is unavailable, the decision may still be taken. Knowing the difference between “need to know” and “nice to know” information help to identify the critical path in a project. Both these categories are considered information.

It is not always obvious if data is actionable, sometimes information is the result of small sets of data hidden away in different studies. The finding and combining of these data, tagging them as actionable for a decision, will help others understand the use of the data and information used for making a decision.

3.1.1 Information needs: measuring the success of a project

The RO’s goal is to develop a drug as long as it is a potential success. The means to reaching this goal is to run a drug development project. The goal of this is development project can be defined as follows: “successfully developing a drug as long as it is a potential success”. As the definition of success is unique per project, it has to be set for each project, preferably at the start. Success, even if clearly defined, can come in many different forms, as outcomes may differ from the expected result but still be considered a success. In order to better track if the project is still a potential success, success factors must be precisely defined. To find out if a goal is reached, information on the performance of the compound and the project itself is needed. In this section, the information needs to measure the success the development project is analyzed, which requires the projects to be analyzed using the project management theory.

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5 More information on this can be found in section 2.1.1: Research Organizations
Project management in theory

For the project, a goal is set and the way to reach that goal is determined. This results in an a number of actions that will progress the project to its goal. In classical project management, a project’s success is measured by three factors: Time, Budget and Results [Meredith, 2006]. The factor time is used to track the progress of the project with respect to time. There are various methods to do so, but most include a form of presenting the planned and actual progress of actions based on the time they occur. Financial resources are measured in a similar manner, but now the actions are measured the costs and benefits. Again the difference between estimated and actual resources is most insightful in showing the quality of success of the project and its planning. The last factor is results, i.e. the “deliverable” of the project: they are the outputs of the planned actions during the project and can be used to verify if these were done according to the plan.

Each of the factors is measured by actual comparing the result to a set objective. To verify the goal was reached, information on time, budget and results is needed. Project information needs using this method are as shown in the table below:

<table>
<thead>
<tr>
<th>Project management success factors:</th>
<th>Time</th>
<th>Budget</th>
<th>Result</th>
</tr>
</thead>
</table>

Table 3.1: Project management success indicators

Applying theory to drug development projects

Managing drug development projects is more complex than is supported by the usual project management theory. As with theoretical project management, the planning and controlling of a project is done by the analysis of the project’s actions and results. As one would expect, the actions are checked to see if they were done according to requirements and plan. In case of drug development, this is not sufficient to guarantee a project’s success. It should be noted that the quality of the information revealed by a project step is not necessarily related to the research quality of that step, especially when the information is related to the effects of a compound: the effects of a compound are not a result of the research, but of its chemical properties.

A superbly run study, done completely by the book, can show results so dismal it requires immediate termination of the project. The other way around is also possible and is actually often used: if a study was found to be below legally required performance standards, this may still progress the project. While that particular study might have to be rerun to provide “official” data, the project may be progressed to the next step as the information of that study will be known. These different qualities of studies may be used tactically, non-GLP or non-GMP studies are run first to find results cheap and fast, and will be followed later by a GLP/GMP version once it is known the outcomes will be worth the investment.

Instead of using that Information on time, budget and quality, the project team uses information about the compound. Not only is this information used to determine whether a compound is worth continuing the project, it is also used to determine how the project continues. As it is the goal of the project to gather information on the compound’s effects, the actions to provide this information need to connect to the compound’s unique nature. This requires a unique combination of studies per
compound. As more effects of the compound become apparent, the required research can be determined more accurately. New information is therefore the cause of changes in many project phases. It can cause minor changes, such as measuring an additional parameter in a study, to significant changes, altering the project plan by changing the studies. Information can also affect the whole project, as the outcomes can require a re-evaluation of the compound’s (and thereby the project’s) viability or an adjustment of the project strategy. This changes the task of managing a project from guarding the project plan to defining (and then maintaining) the project strategy. Time, budget and quality of actions is used, but mainly to set boundaries and requirements.

**Translating drug development practice to project management**

In the section above, it was shown that running a project well does not guarantee the success of a project, nor does just having a good compound ensure a successful project. To be a success both the project execution and the compound must be of sufficient quality. To determine the status of the project and the compound, the information on both these topics needs to be tracked. To support this, instead of using the factor project results, the project team will have to use two types of information: Project success information and compound success information.

![Figure 3.1 Information distinction: compound and project](image)

**Project success information** is needed for measuring the success of a project’s execution. It manages information about time, finance and execution, and the objectives set to those factors. The theoretical budget and time management occur here, as well as a check on the quality of execution of each action.

Action execution information measures whether research was done according to the requirements. This consists of two aspects, whether all the information required for official documentation was gathered and if this was done according to the required regulations. A second test is that of data output fit, it measures if the data that results from a study is what was required from that action. Where the former factor is a check whether the study was executed well, the other is a check to confirm a study was designed well.

Failure on this criteria will require an adjustment of the planning, possibly requiring a reiteration and re-allocation of project resource. Information of this type will be called project information.
**Compound success information** is used for measuring the success of the compound. It is about the compound and its effects and the objectives set to it. This is only information on the compound, only either to evaluate the compound’s success or to determine what further actions are needed to complete its development. Information of this type will be called compound information.

Early in the project, general safety tests show what kind of adverse effects can be expected. This compound information sets the requirements for studies specially designed to research those effects and influences the parameters measured at every study later on.

It is possible make this distinction between project performance and compound performance with respect to all of the project management categories time, budget and results. Compound production time and compound creation costs (the factors time and budget) are as diverse then the compound’s effects and are also used to decide on steering and management issues. During a project, the fabrication time and cost of a compound are constantly changed as better production processes are invented. The information regarding these two factors is used in the selection of the amount of substance tested and the location and size of tests, and at a later stage to see whether the product will be economically viable. Using these additional factors will change the classical time, budget, result measurement to the table shown below:

<table>
<thead>
<tr>
<th>Project management success factors:</th>
<th>Time</th>
<th>Budget</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project information</td>
<td>Project on time, studies in the right order</td>
<td>Project budget information</td>
<td>Quality of work done</td>
</tr>
<tr>
<td>Compound information</td>
<td>Compound production time</td>
<td>Compound creation costs</td>
<td>Compound effects</td>
</tr>
</tbody>
</table>

Table 3.2: Project and compound success indicators

### 3.1.2 Different scopes of information

Any development creates a lot of information on the compound and on the project category. It is unlikely that all information is equally useful to determine the success of the project however. To determine whether there is a difference in the informational value for the purpose of determining success, an analysis of how information is used will be made.
In the actor analysis in section 2.1 it was shown that different members of the project team use information differently. The project leader will determine the effects of an action on the whole project, while a department representative will determine what effect this information has on studies performed for his department. According to project management [Meredith, 2006], different layers in the project management should be responsible for their own part of the project, with the project leader as final responsible person. This does not mean that the project leader is required to know as much detail as the project team does. In order to prevent information overload, it is often best not to know the details unless the situation demands this. Project members focus on different aspects and require different levels of data aggregation and data topics when reviewing the results. The segregation in this level of detail is not only encountered when (re)viewing information, it is also present in controlling a project. Many of the lower level decisions can easily be made by researchers, developers or department members. In that case, presenting all information to everybody would probably cause information overload. In normal project management, presenting the decisions is sufficient, only when verifying a decision more detailed information is needed.
Defining information scope

The difference in levels of information detail enable decisions to be made at the correct level. It prevents project members being overloaded with detail, yet can still provide all the information used when needed. Detailed designs for studies are made by project members without guidance of the project leader. These designs require knowledge of that particular field, sharing this expertise would not add value or speed to the project. Higher level decisions are made in project groups, using higher level information to overview the project phases. At the top, there is generic data on the whole project and its timing. Describing the information use encountered at Kinesis, different management layers can be identified [Beroggi, 1999] can be used to categorize these levels of information. These are the layers: strategic, tactical and operational.

**Strategic** information is information needed to frame the development strategy of a project. Taking compound and project category information into account, strategic information is used to determine the success of a development project, including the success of the compound. Additionally, information is used to set boundaries to the project. These are mainly factors outside the project team’s reach, such as total available budget, the safety requirements of specific types of compound and existence of competitors.

**Tactical** information is used to plan all the project actions (studies, analyses, meetings, decisions, etc.) which are needed to execute the development strategy. At this level, the selection of actions is mainly based on compound information, while project information is used for the final planning of the actions.

**Operational** compound information consists of information about the effects of the compound, and is mainly used to design studies. Operational project management information is gathered from any action to measure the progress of individual actions.

These layers are hierarchical, with the lower layers providing the information for the layer above it. When using the information of the lower level to create higher level information it is aggregated. This means that information is gathered to find trends and averages. While this will give more insight and span more topics, details of the information are lost.

To determine the success of a development project, only a part of the total information is needed. This is the strategic part of the information. However, when guarding the development of a compound, just measuring the success is not sufficient. While the strategy dictates to what extent a project and compound are successful, it does not inform the project team what research is needed. It is the lower level information that is used to run the project and develop the compound.
Blending the information scope into project and compound information

Controlling a development project is done with two types of information. One is the compound information used to measure the compound, the other is project information used to measure the quality of project execution. This distinction is not normally used in project management, as it is just the quality of a project that is used to manage project. However, in drug development projects, these two information types are used throughout the development project.

**Project information** consists of the strategy and the objectives that need to be reached. These are the highest aggregation of budgetary and time information available. The overall budget and time planning are shown here, whether a project is on time, on budget etc without going into details why this is so. Another example of this strategic information is whether there is a competitor developing a similar compound and if so what the time schedule of this competitor is.

The tactical layer consists of the budgetary and temporal design of studies within the project phases, as well as their actual costs. At Kinesis, time planning and cost planning are currently separated, the tactical level of studies is presented in a different application as the financial overview, both example of tactical information.

Operational project information is outside the scope of the thesis, as the operational actions are all outsourced. The different departments and CRO’s use the operational information internally to design and manage studies and actions, so while this information is needed, it is not shared with the project team unless asked for. The department representative will verify the data, but operational information is not used to steer the project.

**Time information:** Time planning is very difficult in drug development. This is mainly due to the fluidity of the project. Delays, as harmful as they are, are usually not the main concern. The main concern is having to re-plan a project due to unexpected outcomes or changes to the drug product. With such uncertainties planning beyond the current phase is less useful. Currently planning is done for an entire phase with Gantt charts and time tables. This does currently not include other scenarios, when unexpected changes occur.

**Budget information:** Kinesis itself does not procure the budget for the development, this is done in accordance with the sponsor. Generally a project is designed using the research requirements and then is filled in according to the available budget. Tactical changes include selecting specific CRO’s and placing non path critical studies at different times in the planning.

**Result information:** Result information has two sub categories. The first is if the action was done according to the specifications given by Kinesis (or the RO) to the CRO. The second type of information is whether the specifications given are what the project requires. If either of these do not meet up to requirements, the action’s result can be less, if not totally, useless.

To manage a project, controlling is done at the phase level, making tactical information the most needed information type for control. The operational level of project management is often not needed as these actions are outsourced.
Compound information

Compound information is managed similarly to project information, but has different topics and different usage. As project information, compound information is structured by topic, these are efficacy, safety, CMC and ease of use. Each of these aspects informs the team on a vital part of the compound performance.

**Efficacy:** This category of information manages the beneficial effects of the compound. At the strategic level, this is done by presenting the primary pharmacological use. The use is expressed by the effect the compound has on the indicated clinical condition. At the tactical level, efficacy information is needed to find what studies need to be performed to analyze efficacy and make compound decisions, such as to set the dosages and select the lead compound. The operational information concerns factors like rate of intake and removal from the body and the dispersion of the drug throughout the body. For different compounds different parameters will be measured, in different ways. What is relatively simple is that for each project there is a single expression needed to measure the efficacy. This is because for each project, generally just one goal or mechanism of action is researched. If a compound is deemed useful for other clinical conditions, either the same parameter is used against a different condition, or a new (sub) project is started with different criteria.

**Safety:** Safety information concerns all information about adverse effects a compound can have. Adverse effects are all effects that are not sought after, and are considered to be negative effects. This is the most difficult category group of information to track. The difficulty lies in identifying all the correct safety parameters. There are more or less standard safety parameters which should always be checked, but one may never assume this is a complete list. Analysis of the clinical condition, compound type and targeted population need to be done to find the full set of safety requirements. This requires multiple experts of different disciplines. When measuring at the strategic level, safety aspects are tested to the maximum tolerable level, set for the project, as well as compared to any competitor products. On the tactical level, information in this category dictates the studies done in the first two phases of development, the Non-clinical and clinical phase 1.

**CMC:** CMC stands for Chemistry, Manufacture and Control. The information in this category has to do with the production of the compound. Production methods, substances added to a drug and the method of administration are all factors that are managed in this category. The strategic level of this information is rather small, it is not really used to set standards in the way that safety and efficacy do. On a tactical level, this category is all the more important, as almost every change in the compound, its production process and the method it is administered will be cause for new safety and efficacy tests. Operational information is the amount that can be produced, the time and costs this takes.

**Ease of use:** Ease of use information concerns information on the user requirements of the drug. This concerns formulation, the rate of use per day and the adverse effects it has on a user. While these look to be part of previously mentioned categories, the grouping of this information here is done to
check whether or not a compound will be used once it is available. Ease of use factors are very important to the consumers\(^6\), so much so that it will affect the development of a compound.

The highest level is the strategic level, which is needed to express the key performance parameters of the compound, stating the degree of success. At this highest level the information is divided in aspects of the drug’s working. At the highest level of the project management, these aspects are used to verify whether a compound scores within the required levels, which is done by comparing the information to the objectives.

<table>
<thead>
<tr>
<th>Results</th>
<th>Time</th>
<th>Budget</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Compound results:</strong></td>
<td>Compound results:</td>
<td>Compound results:</td>
</tr>
<tr>
<td><strong>Efficacy, Safety, CMC, Ease of Use</strong></td>
<td>Production time</td>
<td>Cost to produce the drug, Cost to produce the formulation</td>
</tr>
<tr>
<td><strong>Project Management results:</strong></td>
<td>Project Management results:</td>
<td>Project Management results:</td>
</tr>
<tr>
<td><strong>Information quality, information progression, information reliability</strong></td>
<td>Project planning, time overruns, strategy compliance Risk</td>
<td>Cost to run studies, costs overruns</td>
</tr>
</tbody>
</table>

Table 3.3 Examples of project success factors

No operational levels were shown, this is because strategic and tactical levels are used by the whole team, whereas operational information is needed at the department level. This distinction is made in order to be able to model this difference. Not only is the information divided in different compound aspects, the information is also divided by department. Each department has its own knowledge and expertise, which affects the information needs. In chapter 2, the different departments were introduced, these are non-clinical, clinical and CMC. Each of these departments requires very different knowledge, even if they are working on the same phase.

In toxicity studies, knowing a study is clean (there were no toxic effects found) is all the information required to continue. If adverse effects were found, all the information on the kind of effect, the strength of the effect, the chance of occurrence and many more details become necessary to know.

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\(^6\) As stated by the Kinesis drug development teams.
3.1.3 Information sources

Compound and project information have different sources and is needed by different members of the team. One can tell much from blood samples, but not how much the study has cost or how long it took, nor is this needed to analyze the success of the compound. To measure the success of the project, this is needed, so reports on the organization aspects have to be provided. Though the sources and the format by which the information can be found differs, both types of information have in common that they are not readily available. In both cases the information is actively transformed into meta data from data. For each type of data, this is done in different ways.

<table>
<thead>
<tr>
<th>Project management success factors:</th>
<th>Time</th>
<th>Budget</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound information</td>
<td>Operational</td>
<td>Operational</td>
<td>Strategic/ Tactical/ Operational</td>
</tr>
<tr>
<td>Project information</td>
<td>Strategic/ Tactical</td>
<td>Strategic/ Tactical</td>
<td>Strategic/ Tactical/ Operational</td>
</tr>
</tbody>
</table>
Compound data is generated by performing studies. These studies, done by CRO’s, produce an incredible amount of data, mostly in the form of tables with observations. This is not yet information, this data is a total of all measured values during a study.

Compound meta data is the results of compound data analysis. Resulting from these analysis, done by SSC’s, reports are written with data and meta data in these reports is focused on the study, it is not framed for complex decision requiring data from multiple studies.

Compound information is that selection of the data and meta data that is used in decision making. The information created by the project team, they identify the need for the meta data and, if needed, transform it from reports, to find the information.

Project data is generated by every action in a project. Data for a project is the time of every action, as well as the cost of the action in money and time. As specified above, the quality of execution and the fitting of the action in the project plan are also project data. Due to the nature of projects, every action planned generates data by executing (or not executing) it.
Project meta data is generated by the project leader [Meredith, 2006], it is his task to have an overview of the status of the project, which means in this case the project management parameters. Gathering the data about the actions, such as the start date and the end date of an action, the duration can be calculated. This is further transformed as it is compared to the planned start and duration of an action to verify if the project is on schedule.

Project information is generated by the whole project team. Project information is a result from compound meta data and project meta data, analyzed by the project team to find answers to current and upcoming issues in the project. To get this picture, both compound and project related meta data is needed.

3.1.4 Information aspects: Uncertainty and importance

Currently there are three dimension of data and information. These are the type of data, either project or compound, the level of detail, operational, tactical, strategic, and the level of data to information transformation, raw data, meta data, information. To explain how data is needed, two more dimensions have to be added. This need is explained in the example below.

In the above description on the use of informal data, it is shown that a project team will have access to a preview of the results, which are internally used to manage the project. This information is not presented to any of the external source, until it is formalized the information is shared. This introduces two additional dimensions of data, the formal/informal dimension and the internal/external dimension. These two dimensions were introduced by [Krishnamurthy, 2006] in his modeling of data when building information systems.

Accuracy of information

By nature, the measured compound information is inaccurate, it is the measured effect a compound has a unique environment, the human body. Each human is different and this is a factor of importance in measuring data for research. As each human will react differently on a drug, the actual effects cannot be stated from measuring individuals. The effect strength and any additional effects present can be estimated by measuring a large amount of subjects, which should cover the ranges of outcomes if the population is large enough.

Formal/informal information

Data can reach the project team in different ways. The formal way is gathering data from a study, and then analyzing and written into a report as meta data. This can then be analyzed to find information so decisions can be made. This is the use of formal information. Data gathered during a study is presented to the project team so these can forward it to an SSC to analyze and write the report. During this analysis, the project team itself will also analyze the data, which results in a preview of the results. Using this preliminary information, Kinesis has the option of adjusting
planning and designs. The preliminary information is informal information, it is not as accurate or well structured as formal information, but it can be used to make decisions. The decision made on informal information will have to be verified with formal information however. Only the formal information and the effects it has on a project will be presented to the sponsor.

The arguments behind the formal/informal distinction is that if a system is not able to cope with informal information, this information will not be inserted and the system will lag behind the project or will be incomplete, adding less value than its potential. In drug development projects, the difference between GLP/GMP and non GLP/GMP is another example of the distinction between formal and informal information.

Being able to model the formal and informal data allows a better fit to the actual management of a project, since both versions of data are used. In using informal data, not only is the decision making faster, also difficult to verify data and environmental effects can be modeled.

**Internal/External information**

The distinction between internal and external data is the difference between data having value outside the immediate process in which it is used. The internal information is considered information used to make decisions in the drug developer’s circle, whereas external information is considered information to inform and report. It is an important factor in the communication of data. Since the decisions on many topics are made by the sponsor (as will be shown in chapter 3.2), who has to use formal information, this data is not external.

The link between internal and external and informal and formal is not always present, the assumption another company is developing a drug for the same market can be informal information, but is considered external information as it is used to set the development strategy.

Knowing the outcomes are an accurate representation of the effects the drug will have when marketed is a powerful factor in making decisions. This accuracy is increased as larger scale tests are run, which is usually done later on in a development project. At the start of a development, this can lead to uncertain data, as tests are too small to give confidence in the accuracy of information.

In drugs, effects that have a one in a million rate of occurrence are possible as the total of subjects tested is in the thousands, one cannot assume that these will be found during the development phases. The largest test use some thousand patients, which makes it probable most of the effects are found, but not certain.

Uncertainty is encountered in three ways, the up to date factor of the data (one of the issues identified by Kinesis), the fit to needs of data to information need and the accuracy of the data. Each has the same effect on the project, increasing the risk when making decisions.

One way of making sure the data is as new and up to date as possible requires a centralized data management system, which is currently not available. This central system will be able to find the
different data, no matter what topic or department they originated in and gather it to the central system.

The certainty of fitting data is harder to support, as it requires a lot of expertise. One method of supporting it is a logic system that builds up information from meta data and data. If the information parameters can be expressed in the meta data (and one step below that, data) parameters, the certainty of data can be increased.

Showing the accuracy of data is possible though directly increasing it with support is not. This is done by finding the average effect the drug has in the whole test group. Larger studies will give more data, which statistically gives a result closer to the actual value. This accuracy can be expressed in the amount of times the parameter was measured. This increases the accuracy and the level of confidence one can have in a result. This will not only increase the accuracy of the value, it will also allow for a larger confidence in the results. Some factors are more often measured than others (for operational safety requirements for example), allowing certain factors to have more accurately measured compared to others. A way to measure this is to show how many subjects were tested for that parameter. Combined data of multiple trials generates more certainty than a single trials, so if the data gathered from different studies can be used for one topic, this should be added to the information.

Blood pressure is a parameter that is measured at every clinical trial. This is done during the first clinical trials, which has an average population of around ten subjects. When a simple phase 2a trials is done, with around twenty subjects, the results of the blood measurements can be compared to get results of a total group of thirty instead of the population of largest study, which had twenty subjects.

The importance of information for each decision is subjective. Outcomes influence the importance of information, but the mechanism is too complex to model. Currently only the research team has the expertise to define the importance of information. The importance of information is not always obvious, even if the information need is known. Even if the difference between need to know and nice to know can be clear, the specific importance of different parameters of the same category can vary. Each piece of information has a base importance, which is altered by the difference the information is from expected. This difference is the realm of the expert of that area, who is best qualified to measure the difference between information. When discussing information and decisions, being able to communicate this difference can help make better decisions, so a method to rank the information on importance should be done. This is currently done by having the expert inform the project team during the meeting. This will not be directly possible if the information is presented in a system, so a ranking or importance factor should be able to be modeled in information.

Transformations can require several steps and incorporate the data of several different studies to create meta data. Resulting from these transformation will be data in the form, graphs, averages, tables and textual summaries and conclusions that show aspects of the compound.
3.1.5 Managing information

Information is not static nor uniform, it can be presented in numerical, textual or visual representations of data and is continually in changing. Information needs to be up to date. It needs to be the newest and best available data. This means that the project team should always be on the lookout on updates and changes in data. Considering the amount of data available and the specific conditions that make data information, this is a difficult task. New data does not present itself as an update of a specific parameter, it should be found to be such an update. In drug development, old data can be less accurate, or even point into a different direction. As [Krishnamurthy, 2007] stated: “Not recognizing and recording this change can render old data, which was accurate or right when recorded, useless or ambiguous at a later date”. In an industry where such as the drug development, this especially true.

In order to come to information, the required metadata that needs to be available has to be identified. This means that the steps of transforming data to information need to be known to the project team. Not only should the project team know what information is needed, they must also know what data is needed to create the information (study parameters) and how that data can be created (study and study outputs).

The effects of changes of information can be significant, changing the best alternative or the options available in a decision. These changes can be for a single decision, but can also influence a whole project and its viability. The changes occur due to the uncovering of additional data, old data is appended, replaced or supplemented. The aspect that makes information out of data changes per decision and moment in time as well, what is information in one scenario is data in another. The content of information is a factor of making it information as well, dependent on the outcome of a study, more or less information is needed about that topic.

Data and metadata on the compound is stored by the department, on a shared space where the project team has access to. One disadvantage is that the this space is designed for the department, which means it cannot be used for external communication. Since all the compounds data and metadata of a department is stored on their shared area, this is a lot of data to search through. This leads to a second, smaller disadvantage, due to the structure of the department’s shared space, it is difficult to find data.

The compound information is stored in the Investigators’ Brochure (IB), an official document with all the known (and relevant) information on the working of the compound. The document’s main purpose was to submit information to regulatory affairs in an official format, but its use was extended to be the main storage of information on the compound. This document is continually updated as more information becomes apparent.

Project information has no place in the IB, to track it, other methods are needed. There are many options available for keeping track of the project information, either on paper or computerized. The project planning and history is presented in the project management factors, focusing on what has been and what will be done. The main concern is that the two information streams are stored separately, with no option of showing the interaction of the effects of them. This is the cause of the third issue, showing the interaction between studies outcomes and project plans. The systems for
storing compound and project information are highly specialized, which allows no room for the high requirements the pharmaceutical industry demands on the flexibility.

Figure 3.4 Information exchanges of the actors
3.1.6 Analysis of the information used in projects

After analyzing the way information is used and presented, the following aspects of drug development projects can be stated:

It was shown that making the distinction between the information level is needed to be able to determine what information is needed to gain insight in the status of the project, i.e. without information overload. As the original assignment was to determine whether it is possible to support a methodology that guards the development, this difference in information needs to be taken into account when creating support.

**Information used is complex**

The complexity of the information makes it impossible to automate the determination between the difference of data and information. This will require the project members having to identify the information from data themselves and present this as information to all other members (and the system). The complexity stems from the large amount of guidelines and four non static qualitative aspects. It requires intelligence (i.e. a human mind) to determine what the information is and what isn’t.

**Information complexity is structured**

The nature of the information is that the information categories can be identified using the methodology presented. There are two distinct information flows, each with three subcategories, in each of these flows and categories there are at least seven topics that are used to measure success. While this will not help determining what is information, once structured it will help apply the project team apply their expertise to a more concentrated area.

**Information and (meta) data are stored using different logics**

Data is currently stored diffuse, per department and on study, where as information is stored centrally, per project and topic. This duality creates the danger in the inability to link data to information and the inability to gain a clear overview of the data. This in turn makes it more difficult to find the data and guarantee the up to datedness of the project information.
3.2 The project controllers

Of all the people needed to develop a drug, only a small group is in charge of the development. This small group is the project team, a team of experts that together should have the required skills and knowledge to define the information needs, understand the effects of external constraints and control the project management aspects of developing a drug. To be able to manage the specific project and information architecture, the project team has a structure that is designed according to the project phases and information structure. This is done by creating roles that have a portfolio of tasks for managing specific aspects of the development. A team member is defined by his/her roles, which can be more than one.

Roles come in two categories, the project leadership and the project expertise. Leadership roles are concerned with managing the project, the expertise roles are focused on information generation. Information is not generated by the person fulfilling the role; he heads a department of experts to create and transform data. The role of presenting the resulting information to the project team is called the department representative, as he provides the information generated by “his” department.

The core of a project team consists of five roles, to which more can be added if the situation demands it. These roles are shown in table 3.6, in which each role is given with the category and a short description of the function of the role. More information on these roles can be found in Appendix D: Project team and hierarchy.

<table>
<thead>
<tr>
<th>Role</th>
<th>Category</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project leader</td>
<td>Leadership</td>
<td>Organizes and manages the project</td>
</tr>
<tr>
<td>Sponsor's representative</td>
<td>Leadership</td>
<td>Decision maker (or Decision maker’s representative)</td>
</tr>
<tr>
<td>Non Clinical department</td>
<td>Expertise</td>
<td>Steering the project, design and managing of all non Clinical studies</td>
</tr>
<tr>
<td>representative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical department representative</td>
<td>Expertise</td>
<td>Steering the project, design and managing of all Clinical studies</td>
</tr>
<tr>
<td>CMC department representative</td>
<td>Expertise</td>
<td>Steering the project, design and managing of production, formulation and container fabrication</td>
</tr>
</tbody>
</table>

Table 3.5 Roles in a project

7 The specific content of management is presented in section 3.3: Controlling drug development projects
Decision power associated with roles

Decision making power is spread out over the project team. For many decisions multiple team members are required to provide information inputs and the result of the decision will affect multiple team members, who may or may not have been included in the decision making process. A higher level decision generally affects more project members and requires input from more members.

Decision power corresponds to the three levels of detail encountered in information, strategic, tactical and operational, as is shown below:

Strategic decisions are made by the people from the leadership category. Decisions on this level consist of setting goals and objectives for a compound and for the project as a whole. Decisions on this level are made by the sponsor’s representative and the project leader, where the sponsor’s representative has the actual decision power and the project leader has an advisory role.

Tactical decisions are generally made by the whole team. This is done due to the high requirements on information for these decisions. Many of the decisions can only be made with all departments represented but even if decisions do not require information from all departments, all departments are likely to be affected by decisions of this caliber, so they need to be informed of these decisions.

Operational decisions are action and department specific and are made by the representative of the department in which the action is executed. The decisions of this caliber are mainly made individually, though requirements from other project departments can influence the decision making.

In the figure 3.6 the representation of decision power in the project team is shown:

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8 As was shown in section 2.1, there is decision power outside the project team as well. This comes in the form of the organization owning the project. While the sponsor’s representative has much power to control a project, he often needs to report to his management and receive decisions from them.
The project team is a small network

The fact that information is created by different departments and is not shared automatically makes the project team a small network. This network has an open, interdependent and pluriform setting [de Bruijn, 1999], in which information sharing has no intentional boundaries. The boundaries that create the network are there because of difference in knowledge. While support will not be able to remove this network setting, it should support information sharing in such a way that the negative effects of the network settings are mitigated.

3.3 Controlling drug development projects

Project control is the total of all steering and managing actions performed in projects to bring the project to a successful end. To control a project one requires a clear overview of the actions available (e.g. study types) and in what direction these actions will steer the project. In this section, control options are analyzed to find out how projects are controlled and to determine if control is different from “standard” project control.

To determine how projects are controlled, the definition of project control needs to be set: the actions of making and implementing decisions aimed at guiding the project to success [Meredith, 2006]. Using this definition, control can be seen as a two step process, first the decision making and secondly the implementation of this decision. In this thesis, the scope is focused on the decision making aspect, which is researched to find methods to support it. This will start in section 3.3.1, where is explained how goals and objectives are set. With this information an inventory of encountered decisions in drug development projects is made in section 3.3.2. In section 3.3.3 an analysis of the decisions is made, leading to the requirements for supporting decision making.

3.3.1 Structuring control

With the information needs and availability explained in section 3.1, a way of measuring success must be defined. The way the goals are set and measured shows how information is used to control a project and what demands on the form of information are needed. The project goal was defined as successfully developing a potential successful compound. Methods used to measure this success will be analyzed below.

Drug development projects use terms commonly found in project management theory to measure and manage with. These are goals, objectives, criteria, parameters, scenarios and strategy. However, they may have a slightly different content than some of the theoretical definitions [Beroggi, 1999]. In order to be able to present a clear and uniform presentation of project information use, these terms will be defined below.
Goals

For the term Goal, the following definition is best applicable: “Goals are broadly worded statements about what we desire to achieve in the long run” [Patton, 1993] who states The goal is considered to be the main drive of a project, in our case the reason why a compound is being researched.

The goal of every drug development project is the same: To successfully develop a compound as long as it will be a potentially successful drug. Generic as it is, it shows the main focus as a goal that can be tested yet allows it to be expressed in the full range of required outcomes. Every development project should have “success” as a main goal and continuously test the project’s status to their definition of successful. Failure to do so will result in an increase in risk and wrong development strategies.

Objectives

Again using the same definitions, “objectives are more focused and concretely worded statements about end states” [Patton, 1993]. With objectives, the project team can set measurable targets for any project and compound requirement they may have. In drug development, the objectives are divided into project and compound objectives. The project management objectives are used as boundaries and optimization exercises for the total project, while the compound objectives, called primary endpoints in the Pharmaceutical industry, are the targets set for the compound to reach.

Objectives are expressions, consisting of a parameter, an operator and a level. The parameters are used for time, budget, quality and a multitude of compound parameters. The operator shows the type of comparison (more then, equal to or less etc.) to determine if the objective is met. The levels state the value that the parameter should reach. These levels can be a numeric value, or a

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9 Other authors use different explanations for goals, such as Sage who states a goal needs to be measurable success statements [Sage,2000]. Goals in drug development have many different ways of being considered a success, expressing the goals single measurement is not effective for drug development projects.
comparison to a constraint. Examples of objectives are that the development should be done in less than ten years with a budget of less than nine hundred million dollars.

Objectives in the pharmaceutical industry are continually adjusted: as new information is uncovered, the objectives and even the structure of the objectives may change. This depends on the effects a drug has and how that translates into the potential success of a drug. Reasons and consequences for such changes must be tracked. This is best explained with an example. If a company is developing a drug for a currently untreatable and very serious clinical condition, the objective would be to find a drug that works, with no objective set for adverse effects. During development, another company may market a drug for that clinical condition. The first company then has to change their objectives to find if their drug is still a potential success. No longer can they rely on just some positive effect, they now have to have at least an effect, better than the drug already on the market.

Without knowledge of how a drug will behave, the exact objective cannot be set. The example showed that not only objectives can change during a project; there are different end points of a project which will meet different objectives. As long as the right combination of objectives is met, the project may be considered a success.

These objectives are measured by criteria and selected in scenarios, which will be explained below.

Criteria
“Criteria are specific statements about the dimensions of the objectives that will be used to evaluate the alternatives” [Patton, 1993]. This means that objectives are made up of one or more criteria, which are used to measure if an objective is met. Criteria are used to steer a project, keeping an eye on what should be reached and where the project currently is. The steering is done by making decisions on what to do, evaluating the alternatives and selecting the best option.

The criteria should be set in such a way that they can be used for steering and managing a project. This means that they have to allow the decision maker to evaluate what the current status of a project is and how to select the best option to continue. The way this is done differs per decision and per criterion; also the project information criteria will generally have a different set of steering options than the compound information criteria.

To be able evaluate alternatives; criteria must make the alternatives distinguishable. To do this, criteria are most often presented in ranges, different levels of outcomes that correspond to categories of satisfaction. These different levels of satisfaction have alternatives attached to them. For example, a possible criterion for a decision are whether the ease of use is acceptable or higher. This criterion is made up of a rate of use (a parameter) and a side effect strength (a different parameter). The criteria will be acceptable if the rate of use is less than once per day and the side effect strength is mild or less, either of these parameters being higher results in the criterion being less than acceptable. Generally the qualitative ranges are categorized in types as unacceptable, bad, acceptable, good and very good. One special type of outcome is frequently found in the setting of criteria, which is the knock-out type. This knock-out can be found in the form of a single parameter decision, or a as complex as a multi criteria, multi interaction decisions. The result is the same no
matter the complexity, if the knock-out is met, the project is terminated. Comparing the actual value of a compound parameter to the criterion will result in scoring within a certain category of the criterion quality range.

Different criteria have different buildups, from simple ones with a single parameter to take into account to ones with a number of different parameters that show dependency to other criteria. Again, this is best shown with an example. In order to test if a compound is safe to use, a simple safety test may be used to determine the presence of a specific dangerous toxic effect; if that toxic effect is present, the compound is not safe to use. Here the outcome of the parameter used to measure the criterion is binary, either the effect is there, or it isn’t. To evaluate safety a check is done whether the effect is there or not. When deciding, the criterion will be that the toxic effect should not be present. More complex checks are more common, in which the decision criteria are based on a number of parameters which have different types of expressions of outcomes. To explain how this works, one of the earlier examples can be used, that of cardiovascular safety. The criterion whether a compound is safe with respect to the cardiovascular effects is based on the effects of the compound on blood pressure, the heart rhythm, the muscular effects on the veins and arteries and the effects it has on the blood itself. Not only are there multiple parameters in this example, the outputs of the parameters are quantitative, can affect each other and have very different outcome ranges. As with objectives, the criteria can be met with different combinations of parameters. The criteria to define whether the compound is safe depends on the combination of outcome levels occur. Only the expertise of the project team is needed to make a “safe” decision on the large amounts of combinations possible for criteria. To make things more complex, decisions often have multiple criteria, whose values affect each other just as parameter values of a criterion affect each other.

**Parameters**

A criterion can be based on multiple parameters\(^{10}\), each of which gives information on the performance of the compound. Parameters are quantitative expressions. In order to compare them to the criteria, the criteria levels need to be expressed in these quantitative dimensions as well and be translatable to a qualitative measure. In order to test a criterion, the levels set to measure the criterion must be of a similar dimension of that of the parameter. This requires the transformation of a large amount of data to an expression that is easily understood (even if the consequences reaching the criterion is not).

**Scenarios**

Scenario analysis [Beroggi, 1999] is used to analyze possible futures of the project by considering alternative outcomes of the intermediate results. They are the basic way to handle uncertainties in a project. A scenario is used to ask the “What if” question, asking the project team what the next steps should be if one of the possible futures should occur. Scenarios can be used whenever unknown information is made known, which in the pharmaceutical development is often linked to the outcomes of a study or analysis. The scenarios can then be used to request the project team to focus

\(^{10}\) As stated by the Kinesis drug development teams.
their thoughts on two topics. Firstly, what are all the outcomes that are possible, and the second, what should be done if a specific outcome happens. To perform the first step, the project team should map the important trends and uncertainties. With these, the team has to find the different combinations of outcomes of all these trends. Each scenario is based on specific parameter outcomes. The project team can create the a portfolio of scenarios, based on experience with similar compounds or projects. The qualitative approach is used in favor of the quantitative approach, stating whether a scenario is likely while not giving the chance of scenarios occurring. The second step is easier to make, if criteria and objectives are set, the combined expertise of the project team is sufficient to see what steps are needed and if these are worth taking.

In this figure, the action has two parameters, both with an outcome range of 0 or 1. The scenarios show the possible outcomes of the action. The criteria to continue was set at having a beneficial effect (B=1) and not having an adverse effect (A=0). This means continuing the project only if scenario 2 comes to pass.

**Decisions**

The word decision in the pharmaceutical industry is a very broad term, it may be used to refer to a choice between alternatives, or when making a design, which is a decision with a many degrees of freedom. This includes the selection of parameters to use, criteria levels, phase design and project strategy. Decisions are made on the basis of three inputs, criteria, results and assumptions. Criteria are tested with formal or informal information backed up by studies. The assumptions are something
that is taken as true without testing it, because testing is infeasible, or because budget and time do
not allow for testing. Based on the criteria, results and assumptions, a decision can be made how to
continue the project. The options available to the decision maker differ per topic of the decision and
are influenced by the amount of preplanning and predictability of the outcomes of a decision. One
option always available to a project team is to reevaluate the situation and design a new phase or
project plan.

**Strategies**

The strategy of a project is based on objectives set to the project. It is a combination of objectives
that will reach the project goal. The objectives are set from all the compound and project topics, so
there are objectives for efficacy, safety, CMC, ease of use, time, budget, execution and more if
additional topics were deemed important for a project.

For the objectives, a number of requirements are in place. The objectives must each perform well on
their own, but more important, but be a valid combination of objectives. The fact that the objectives
must have their own minimum level is often set by external influences, such as regulations. If these
external requirements have been taken into account, it is up to the developer to set any combination
of objectives as the project strategy. This can mean he can focus the development on any of the
compound or even project management objectives during the development. In most cases, the focus
is set at one specific objectives, such as efficacy, and other objectives are considered to be more
flexible and are adjusted when information on the topics is revealed. As long as a compound reaches
the standards set for the strategy, the project is viable. If the objectives cannot be met, it does not
mean the compound is not viable, it means that the current strategy is not viable.

Strategy has the power to (slightly) influence the compound performance by having effect on the
formulation decisions. If objectives are not met, formulations can be changed to try and meet the
objectives. In this case, the information need (to find a new formulation) is the result of the strategy.
3.3.2 Decisions

The decisions encountered in drug development projects are as diverse in scope and content as the information of projects. Decisions range from setting the objectives for a project to the planning of an individual action. This makes supporting them a challenge unless characteristics are found to structure them. To do this, an analysis of the decisions is made in this section. The analysis will start with a listing of the decisions encountered in drug development project. These are then analyzed to find the structural aspects of the decisions that will show how these decisions can be supported.

Decision mapping

In this section, the decisions found will be ordered according to topic, starting with the creation of a new project and continuing with decisions about which information has to be collected, what actions are required to get that information and finally how all these actions must be managed.

Project creation

Project creation is the very first step of a project. It starts with identifying the objectives, which allows the project designer to determine what expertise is needed to run the project. With this information, the project team can be assembled, who have the expertise to select and assign levels to objectives. The activities in this step are:

- Identify project objectives parameters
  - Time, budget and quality objectives
  - Efficacy, safety, CMC and ease of use objectives
  - Objectives set by external sources
- Identify fields of expertise needed and the roles these create
- Select project members to fill the roles
- Set objectives and assign levels to them (set the strategy)
- Determine information need
- Plan actions and decisions
- Set criteria for decisions

Both the steps of identifying the objectives and the selection of objectives (setting the strategy) were explained in section 3.1.
Information need determining

Determining the information need is a continuous process during the project. It is the analysis of project objectives and current knowledge of the compound to determine what information is needed to reach the end of a project successfully. These decisions are open in nature; there is no fixed list of answers for the decision. When determining the information needs, the followings steps are taken:

- Determine compound characteristics
- Determine constraints set to the compound by internal and external influences
- Transform the constraints and objectives into research questions
- Adjust research questions due to progressing insight (during the project)

Planning actions

Once the needed information is known, actions can be planned to create this information. In some cases, multiple actions will be able to provide insight into the compound, in which case a selection of actions has to be made. Making this selection requires compound information to determine which studies and analyses are needed, followed by project information to fit these actions to the project management objectives.

- Inventory what actions provide answers to the research questions
- Determine constraints set to research the compound and dependencies created by the compound and project characteristics
- Decide which actions to use if multiple actions can provide the answers to the research question
- Design actions (study, analysis, decision and meetings)
- Create the development plan: plan actions in the project path

It should be noted that just as the information needs change during the project, so do the actions. Whether the actions change is not only dependent on the information need, but also on the project management objectives. While the steering aspect of determining actions is the most important aspect, alternatives that provide the same compound information outcome can be selected based on project management information.

Planning the actions is done using the critical path method [Meredith, 2006]. Using constraints and dependencies found from external and internal requirements, the selected actions are organized into the project path. Due to the uncertainty of the outcomes, this is usually only done for the current phase.
Decision on the compound

During the development of a compound, the drug product is designed. This consists of making decisions on which compound will be used and how the compound will be provided. Compound decisions are closed decisions, information inputs present limits to options the project team can choose from when designing the drug product. Most options in the outcome range can be categorized in preplanned decision options. A list of compound decisions can be made, which is shown below.

- Select lead compound
- Select formulation
- Set dose range
- Set dose
- Set clinical condition
- Set indication

Project guidance

During the project, decisions are made on how to continue with the project. These decisions are made using information concerning the progress of both the compound and the project. Decisions to manage the project progress are made on the following topics:

- To start or stop an action
- Select the next actions in the project
- To go to the next phase
- To re-evaluate the project and redesign it
- To change the project strategy

Selecting the next step in the project is a decision that is made periodically, when all the results are gathered to analyze how the project should continue. These decisions normally have four possible outcomes: to continue with the current planned course of action, to select a different (pre planned) course of action or to design a new course of action. This third option is essentially part of the redesign decision. The last option available is to stop the project, which is selected if there are no viable alternatives.

(Re)designing part of the project is an extreme measure to update the project to the results, it can require all the decisions encountered in the categories Project creation, information need determination and Planning action to be redone. Redesign decisions does not always require a complete redesign, it can be as simple as changing the start date of a study.
3.3.3 Decision characteristics

In this section the decisions found in section 3.3.1 are analyzed to find what the characteristics of decisions are. Defining these characteristics enables the decisions to be modeled and supported. This starts with making an analysis of the characteristics of the decisions.

Information use in decisions

Decisions use different kinds of information. Using the list of decisions and analyzing what kind of information is necessary to make the decisions, it appears that the compound information is used much more than the project information. Also the way information is used can be different. Compound information is used first to identify what needs to be done, whereas the project information is used to determine where, when and occasionally, make the selection if there are multiple actions available. This difference in the use of information shows that the distinction between compound and project information is important for drug development projects, contrary to “standard” project management; information outside the scope of project management is used to guide the project. To acknowledge this distinction in control, a difference is made in steering and managing a project. Steering is controlling a project based on compound information and is used to find out what compound information needs to be found. Managing is controlling a project based on project management parameters, ensuring the project is kept inside the time and budget constraints.
The level of detail to which a decision is targeted affects the structure of the decisions as well. The decision to design a study or a complete phase is very different in scope. Depending on the level of detail, different decisions makers are needed, information use is different and the information sharing has to be managed differently.

The internal working of decision making

The way decisions are made are very difficult to formalize. Expertise used in decision making is currently not understood well enough for this to be modeled. It is possible to present inputs and outputs, but not the decision making itself. This is because during decision making, all the criteria are evaluated simultaneously. While the human brain can comprehend the interaction effects criteria have during decision making are too complex to model for every decisions, this will take too much time and as it is not the main goal of the research, will have too little benefit.

Decisions output

The output range of a decision changes the mechanism with which a decision is taken. Decisions can have two types of output ranges, a closed range, which has limited and selectable options, a semi closed range, which has a very large number of selectable options, and an open range, which has unlimited options, or options that need to be created during the decision.

The difference between structuring the outputs of a choice and a design decisions are completely different. Where choice decisions have a limited range of options and outcomes, the design decision is an open ended action.

Decision planning

Decision planning is determining which are the control points of a project. During development projects, the possibility to influence a project is not always available. The point in time when it is possible to control a project is called a control point. These control points are very dependent on the design of the project; most of them must be planned. In this planning, it is important that control points are not only placed at the right time, but also that they are visible long enough before the actual decision to allow the project team to prepare for them.

Three different control points were discovered in the decision making at Kinesis. To guide a project as well as possible Kinesis places control points at events, ends and starts of studies and such. These event driven control points are discrete triggers, an event causes them to appear. A second method for Kinesis to monitor their projects was during periodic meetings. These bi-monthly meetings are used to discuss outcomes and results that did not have immediate impact on the project, these control points are continuous, no discrete event is needed to trigger the control point. The last control point type is the unplanned control point, unplanned control points occur when decisions need to be made that could not be predicted. These are often the result from influences outside the
power of the project team, such as unexpected results or changes in sponsor’s preference. Control points affect the project planning, because of them, decisions have to fit in the following planning categories:

- Event driven decisions
- Periodic decisions
- Unplanned decisions

**Analysis of project control**

Based on the way project are controlled, the following aspects have to be taken into account for designing support:

**Controlling a project is done based on current success**

The information used to measure the success of a project is used to steer and manage a project. Not only is the information used in the same form, the categories and topics, it is (often) the exact same information. The information used to measure success is accurate enough to make decisions on alternatives.

**Controlling a project is a complex, structured process**

The information measuring is done with structured mechanisms of comparison. Information is compared criteria expressions to decide the best option for the situation. Modeling the information can be done using mathematical expressions, the outputs of which can be used to select between alternatives.

**Project members have specific decision power and responsibilities**

This does not only set requirements for the decision making rights for projects, it also forces the information to be modeled as being necessary for specific project members as well as for decisions.

**Decision making is a semi-structured process**

Decision making mechanism varies based on level of detail, but each is formalized in methodology and outputs. The participants, needed information and decision outputs can all be modeled. The complexity is the results of (subjective) interaction effects, constraints, requirements and weight issues when making a decision.

**Decisions are specialized for their content**

The decisions have content constraints and decision making mechanisms that are highly specialized for the type of decision. This specialization takes form decision templates setting the specific information requirements and output range for decisions as well as the method of comparison.
4  Support requirements for drug development projects

This chapter is used as a bridge between aspects of the drug development and the analysis of the requirements of the tool. First, a summary of the information and aspects of drug development is presented, from which a definition of drug development projects is derived. Using this definition, section 4.1 will focus on how the defined projects can be supported. In section 4.2, an overview of information tools currently available is presented to find if there are any tools currently available to support the drug development projects.

First a small review of what was learned about development projects.

- Section 2.1 shows the projects are set in an multi actor network defined as closed, pluriform and interdependent. This will be called the external network.

- Section 2.2 shows external regulations, requirements and rules placing design constraints on a project. This will be called the external influences.

- Section 2.3 shows the is a standard structure for projects and its gives a description of the constraints this sets. This will be called the project structure.

- Section 3.1 shows what information is and how it is defined. This is called information definition. It also showed the complexity of information consists of content and a management stream of information, both having many sub categories to help classify information requirements. This will be called the information structure.

- Section 3.2 shows that information is fragmented and under control of different members of the project team creating an open, interdependent and pluriform network. This will be called the internal network

- Section 3.3 shows that decisions and the decision making process is highly structured, defined and formalized. But formally modeling the dependencies between parameters in criteria necessary for decisions is too time and labor intensive to be viable. This will be called the decision making process.

- Section 3.4 shows how risk and uncertainty are managed and that this requires feedback loops in results and objectives to manage strategy and project planning. This will be called strategy management.
4.1 Defining support for drug development projects

In this section the aspects found in the section above are analyzed to find available methods of support. The support available will be generic as it will be the support to manage these general aspects, so once these support features are found, the drug development specific content needs to be applied. For this the conclusions found in the analysis sections are used.

4.1.1 General support for the aspects of drug development

The process of management is divided in four phases [Sprague, 1980] gathering information (intelligence), designing alternatives and solutions (design), decision making (choice), and implementation (implementation). In decision and management support, only support for the first three can be provided [Turban, 2005]. It is on these aspects the support will focus.

- Intelligence
- Design
- Choice

Presenting the eight aspects encountered in drug development to the management phases gives the results in table 4.1.
<table>
<thead>
<tr>
<th>Aspect</th>
<th>Phase:</th>
<th>Intelligence</th>
<th>Design</th>
<th>Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>External network</strong></td>
<td></td>
<td>Support different information suppliers and receivers</td>
<td>Enable multi actor action design actions</td>
<td>Support decision power in external actors</td>
</tr>
<tr>
<td><strong>External constraints</strong></td>
<td></td>
<td>The ability to model the effects constraints have on the project</td>
<td>Support action dependencies and sequences</td>
<td>Show constraints effects on decision options</td>
</tr>
<tr>
<td><strong>Project structure</strong></td>
<td></td>
<td>Model the Information gathering order &amp; additional information needs</td>
<td>Be able to design a project that fits in the project template</td>
<td>Be able to present industry specific decision topics and the method of deciding them</td>
</tr>
<tr>
<td><strong>Information definition</strong></td>
<td></td>
<td>Support the distinction in Data, meta data and information</td>
<td>Support the distinction between data, meta data and information</td>
<td>Support and provide different information to users</td>
</tr>
<tr>
<td><strong>Information structure</strong></td>
<td></td>
<td>Be able to model the Information categories compound and project and their levels of detail</td>
<td>Support the transformation of information need to required actions and the planning of actions</td>
<td>Present the ability to provide the right type of information for the right decision</td>
</tr>
<tr>
<td><strong>Internal network</strong></td>
<td></td>
<td>Be able to manage diffuse and fragmented information sources</td>
<td>Support roles and the ability for multiple members to work on the project design</td>
<td>Support Group decision making</td>
</tr>
<tr>
<td><strong>Decision making process</strong></td>
<td></td>
<td>Be able to present structured Information requirements</td>
<td>Support continuous and discrete decision scheduling</td>
<td>Be able to present the decision options as well as support open ended decisions</td>
</tr>
<tr>
<td><strong>Strategy management</strong></td>
<td></td>
<td>Track and update objectives, criteria and parameters</td>
<td>Be able to alter the measurement system</td>
<td>Provide support to adjust project design during the run changes</td>
</tr>
</tbody>
</table>

Table 4.1 Support requirements
4.1.2 Specifying support for the aspects of drug development

After filling in the matrix table of the aspects of management versus the aspects of drug development projects, each of the combinations has set requirements for support. These support aspects are derived from table 4.1 and analyzed in the list below.

Intelligence:

Support different information suppliers and receivers: Networks require special information sharing support, enabling the correct information to be shared in the network without giving support to strategic behavior. Due to the closed and pluraliform nature of the drug development projects information must be customized per actor. This makes it necessary for the actors to be distinguished and the information requirements for these actors to be provided. Advanced support would support the actual mechanisms of communication, such as the creation of presentations and executives summaries. No matter how advanced the support, most communications methods will remain asynchronous.

The ability to model the effects constraints have on the project: Constraints of any kind are information. This information requires tracking to be applied when it is needed, which is during decision making and design. This requires the constraints to be modeled in such a way that their effect on the project options is expressed, and to be linked to specific decision and phases. The external influences can in most cases be modeled by setting minimum requirements and constraints.

Model the Information gathering order & additional information needs: The project structure sets information gathering order. In order to be able to support the structure of these projects, actions in the projects need to be identified as being limited to phases, as well as having constraints which state prerequisites. The project structure also sets requirements to set additional objectives for the goals, these can be modeled the same way as the strategic objectives.

Support the distinction in Data, meta data and information: The data created in the different studies needs to be accessible for verification of decisions, this means that the reports containing this data need to be accessible for the project team. The same goes for information, though the difference with information is that the information should be pushed to the project team, while data should be pulled by the project team. This to prevent information overload.

Be able to model the Information categories compound and project and their levels of detail: Structured information can be supported by databases able to handle scripting to present correct information at the right time. This includes data and information presentation, storing, updating and transformation. Structured information can enable templates, pre-filled actions and structure components to easily track information. Advanced versions of these databases are called neural networks, and are capable of applying logic to help track and find information.

Be able to manage diffuse and fragmented information sources: To handle the fragmentation of the current departments, the system needs a back and a front office. The back office is the fragmented per department, enabling each department to add and retrieve the data and information the same
way as before. For the project team the front office is needed to show the information non fragmented. For the internal network, decision support is comprised of synchronous and direct information sharing.

**Be able to present structured Information requirements:** The decision information needed to make a decision is expressed in the information structure, knowing what information is needed allows the system not only to remind the project team what information they required, but also where to find it or even present it.

**Track and update objectives, criteria and parameters:** The information need requires modeling of goals, objectives, criteria and decisions in order to identify the information need for each of these. For this purpose, conceptual (goal seeking process) and mathematical models can be used. Backward applicability is required to verify if old studies are conform the new information needs and the categorization allows the team to verify changes.

**Design:**

**Enable multi actor action design actions:** The external network is not consulted when designing the project. The only step in which external organizations are needed for design are operational actions, for which the design process is outside the scope of the project, but the design must be linked to the action in the system. This can be done as described in the section project structure.

**Support action dependencies and sequences:** External influences present constraints that require checking and verification. These influence the designing throughout the project. It requires the ability to set minimum requirements and if-then constraints to actions in the project.

**Be able to design a project that fits in the project template:** The interface to design the project has a number of additional requirements to support this. Not only must the actions be able to be placed and linked in a project plan, but the project plan needs to be able to design phases add goals and sub-goals and present the constraints when designing the project.

**Support the distinction between data, meta data and information:** The design of information need is the process of determining how the results can be found to fit the objectives, criteria and parameters. This requires support how data is transformed into information, which can be presented as a general information system.

**Support the transformation of information need to required actions and the planning of actions:** Designing using the information structure is to show the difference between steering and managing. The information need has to be transformed into actions. For this, the objectives, criteria and parameters and external influences need to be modeled in such a way they can be compared to the output data from studies and analysis. With the required information known, the studies that present the output factors that connect with the need are identified as needed studies.
Support roles and the ability for multiple members to work on the project design: The system should be able to manage the different roles project members have. This require the roles to be created, setting information needs and supply. Design in the internal network consists of open, synchronous and asynchronous information sharing. Synchronous design support consists of group decision support as well as asynchronous information management. Asynchronous information sharing can be supported by accessible and structured archiving, email, forums and message systems and wikis.

Support continuous and discrete decision scheduling: The planning of decision requires decisions to be planned according to different methods and normal actions. The event driven decisions can be modeled as normal actions, but the unplanned decisions need to be inserted when it becomes apparent they are needed. The same goes for periodic decision, which are the same timeline as the project, but are unrelated to the actions of the project. Decisions can be designed on topic and stored in a template, to enable many of the more standard decisions to be created easily.

Be able to alter the measurement system: Designing the strategy is being able to transform the goal into objectives and translate the objectives into measurable expressions. For this, mathematical models are needed to express the objectives. These need to be complex enough to support different levels in the objectives. To support changes in information need, a history of the information is needed. This history requires to be backwards applicable and categorized.

Choice

Support decision power in external actors: The blocking and decision power of actors is an influence that affects the project decision making. These influences can be considered constraints that must be tracked to inform the project team how these will affect decision making.

Show constraints effects on decision options: External influences affect the decision making by setting constraints. Constraints can be expressed limiting options in the design and decision making. This can be done as if-then expressions or minimum requirements. To model this the constraints have to be expressed in a logical or mathematical model, which has outputs that provide information to the decision makers.

Be able to present industry specific decision topics and the method of deciding them: Choices in the project structure are bound by the project structure and decision outcome ranges. To support the projects, the decisions need to be modeled using the same structure of decision making. This included decisions having a closed, semi-closed or open outcome range, which is a structure of decision making and pre-generated the outcomes. The structure can be supported by being able to create the decisions as well as the outcomes. This requires a decision creation ability and an outcome creation ability.
Support and provide different information to users (Formal/informal information for decision making): The system will have to be able to manage meta data, which is data on data, to make the distinction between data and information. This meta data consists of tracking when data is needed. The meta data the system should be able to handle consists of different kinds, when information is data, what the status of the data is, whether the information can be shared or not are among the encountered requirements.

Present the ability to provide the right type of information for the right decision: Using meta data on information, it will be possible for the system to provide the information needed for decisions. This can consist of the information itself, of links to where the information is stored in the archive system. This sets the requirement for decision creation to track what information is needed, which has to be expressed in the same way as the meta data of the information.

Support Group decision making: Decisions in the internal network are made by hosting meetings, and are generally done offline. The results of these meetings are inserted into the system to show what was decided who had attended etc. The actual decision making process, done offline, is outside the scope of this thesis, but has options for support as well.

Be able to present the decision options as well as support open ended decisions: The making of choices in the decision making process is known to be a complex process of weighing interacting effect. When these interaction effects are present in a decision, the modeling of the decision making process is of such a complexity that within the current research this was found to be impossible to model or support directly. The outcomes and decision options can be modeled, which will help their decision process.

Provide support to adjust project design during the run changes: Other than the method of transforming the goal to objectives and measuring the objectives, strategy management requires the objectives change to be supported. This is defining or selecting new objectives when old objectives are unreachable. To help create new objectives, Sensitivity analysis, What-If analysis and goal seeking are process types that are used to manage these aspects and these processes or their outcomes have to be supported.
4.2 Current support

In the research request, the question was to find out if the project management of a pharmaceutical project can be supported by a tool that can help guard the correct development of a drug. As the analysis of the pharmaceutical industry has shown, methodologies used in different industries are quite similar to the pharmaceutical industry and these methodologies are supported for those industries. The drug development project management methodology has a number of unique attributes however, which causes that support not to fit the current need. Since other industries are supported by multiple support products to manage their core business, why is there no known tool for the pharmaceutical industry?

Trying to find an answer leads to three possible situations:

- There is a tool, but it is not well known.
- There is no tool, but it can be created.
- There is no tool because it is impossible to create one.

In this section, the first situation is analyzed, to see if there is not a tool that can fill the request for support. If none is found, situation two and three will be analyzed, using the previous chapters as a basis for determining whether support is possible.

The people of Kinesis have worked in some of the largest drug development companies before coming to Kinesis. Even at Kinesis this did not result in the knowledge of specialty tools capable of supporting the current needs. Currently the projects are supported by project management tools as well as network communication tools such as E-room. These tools are used for communication and planning, but not for guarding the compound success. These systems support projects, but even with these tools, the issues described in chapter one are not solved.

Searching for available software, at the Independent Project Analysis a topic on pharmaceuticals was found. Research was done on projects in this industry, but this was focused only on the traditional project management steering and organizational effectiveness [Aschman, 2006]. No attempt was made to support compound information steering.

An analysis of the FDA was inconclusive, it points out that with the increase of technology, an ever increasing amount of compounds is discovered. But this technology progress is focused on the operational level of compound discovery and research, not on the management and high level analysis of the development. The increasing complexity of project will require more management resources and the FDA state that a tool to fulfill this role is needed [FDA, 2007]. They further state that they are unaware of a tool that has such a function, but see an increasing need for it.

Searching for specialized support in found other companies presenting database software with limited management options, such as pk-knowledge base. This tool allows compound result tracking, but has no options to show the effects of the outcomes in the project.

As mentioned, the FDA is currently not aware of software that allows the use of computers to ease the difficulty of the management of pharmaceutical development projects. However, after searching
for software for specific purposes in a development project, software per issue group was found. These include the Project Management software, such as MS Project, as well as specialty compound software for tracking results such as pk-knowledgebase and other software for specific studies. Also software for information sharing was found, in software such as E-room and SharePoint.

The current situation is that there is no tool available to support projects in the manner requested by Kinesis. Searching for companies versed in project support and industry related organizations did not yield any hint of such a tool being available or even of being developed. This leads to the conclusion that the requested features are currently not supported in one system, thus the second and third situations have to be analyzed.

The second and third situation have the difference whether support is possible, which will be addressed now. The previous chapter has shown that the support required for these projects is possible, so the question is whether there are tools that allow partial support and can be used in combination with each other.

<table>
<thead>
<tr>
<th>System name</th>
<th>External network</th>
<th>External constraints</th>
<th>Project structure</th>
<th>Information need</th>
<th>Informatio n structure</th>
<th>Internal network</th>
<th>Decision making process</th>
<th>Strategy management</th>
<th>Total: % (of 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS project</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>+</td>
<td>0</td>
<td>-</td>
<td>---</td>
<td>-7 (-35%)</td>
</tr>
<tr>
<td>Pk-knowledgebase</td>
<td>-</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>0</td>
<td>0</td>
<td>---</td>
<td>+3 (15%)</td>
</tr>
<tr>
<td>E-room/sharepoint</td>
<td>+</td>
<td>0</td>
<td>--</td>
<td>0</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>0</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Wikis</td>
<td>0</td>
<td>0</td>
<td>--</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>0</td>
<td>-</td>
<td>- (-5%)</td>
</tr>
</tbody>
</table>

Table 4.2 Software applicable in drug development projects

Each system can score a + for every fully supported feature. Partial support receives a 0 and no support receives a -. For intelligence, design and choice a mark is given in the same order. For example, a wiki is given +0 = 0 for External constraints. A wiki is capable of tracking any information, but has no design tool that enable the constraints to be measured in the project. Using more than static linking requires considerable wiki programming knowledge, so is possible but not fully supported.

Considering the table above, no tool will really fulfill the need of drug development projects. If multiple systems are used, the best result would be with using MS Project, Pk-Knowledgebase and E-Room, granting a total of 12 (60%) when using the best features of each. Considering that the individual aspects are represented in different products, it is worth researching if a tool can be created to manage all aspects.
5 The support tool

This chapter is the presentation of a tool that uses the need described in the previous chapters. This chapter starts with presenting this tool in section 5.1. The method to create the tool is described in section 5.2. Section 5.3 concerns the validation of the system, it is checked by the potential users on analysis, use and ease of use. Section 5.4 is a reflection on the tool, in which the use and benefits of the system are analyzed.

5.1 The tool

In this section, a mock up version of a tool that would fulfill the needs described in previous chapters is presented. Like the needs, this tool is structured as a two segment system, the design of the project is the first segment and the control of a project during the run is the second. Also in this section, a summary of the uses and options of the tool is presented.

General interface

The general navigational structure is in both segments the same, an example is shown in figure 5.1. On the left of the screen are the main categories of actions, which will present a list of action in the column immediately to the right when selected. This second column are the specific actions in that category, which will raise a creation or control screen in the main screen. This screen allows the selected action to be viewed, designed, edited and updated dependent upon segment.

5.1.1 The design section

The design section is made to be able to easily create a new project. It builds up the project in four steps, which have been ordered to be progressive, this means information from previous steps is used to create successive steps. Each of the steps is accessible at any time of the design so skipped information can be inserted in any previous step. Depending on roles, not everyone has full access to the design section. The project leader will have full access, the sponsor’s client is likely to have no access and the department representatives have low level access, which allows the design of studies. In case a project needs to be redesigned, this section is used instead of the management section.
Figure 5.1 screen Kinesis project control general interface

Figure 5.2 screen Kinesis Project control design
The four categories in the design actions to create a drug development plan are:

**Create team**

Creating the team is establishing the members in the roles needed for the project. Many of these roles are standardized, but projects can require different and unique roles. The creating of the team includes the option to create roles and set the information and decisions rights.

**Create strategy**

Creating the strategy consists of four steps, which are in a sequential order. It starts to frame the project environment, hereafter, the team can create the objectives, which are the project objectives and primary end points. These show all the end states of the project that would state the project is a success. The second step is to add the compounds to the project. This can be a single compound, or a list with potential new drug candidates. The actual creation of the strategy is done as the last step. Here, a selection of objectives are combined into a project set of objectives that will be the boundaries of the strategy. Adding assumptions and logic, with the project objectives, the strategy can be described.

**Framing the environment**

Framing the environment is about stating the relevant information for a project. This is a textual description of factors affecting the project, such as competitor influence, the RO’s definition of success for the project. To this, source material can be linked to be able to verify it later on in the project.

**Setting the objectives**

Objectives are expressions with parameters and criteria that measure if the project has reached its goals. These objectives can be found in constraints set by external sources, or performance or project requirements set by the team. In this step, the goals is to identify and create all the possible objectives. There are two types of objectives, the open objectives and the checklist objectives. The open objectives are the objectives of the project and compound category. The project team can design the open objectives from scratch (as is shown in the screenshot). The checklist objectives enable the team to create a checklist of actions that need to be performed, such as having performed a specific safety test. Setting objectives is done in three steps:

1: Identifying the objective parameters

Objective parameters can be found in different categories, each of these categories can have multiple objectives. The tool allows the creation of objective categories and objectives.
2: Setting the levels

Setting the levels of the objectives allow expressions to be created to measure the objectives. Objectives can have multiple expressions to cover the range of requirements set. In case there are multiple objectives with which a compound or project is considered a success, these are all inserted here.

3: Checklist

Checklist objectives are not measured by content output but by a check whether or not the event has occurred. These can be set for project actions or compound information. An example would be: NDA submitted.

Adding the compound to a project

In the step “Adding the compound to a project”, the compounds to be researched during the project are inserted in the system. Information on the following topics is inserted: compound trade mark name, compound chemical name, the chemical formula, a picture of the molecule, mechanism of action. Knowledge from previous projects is inserted here as well: known effects and effect strength, clinical conditions, and indications.

Creating the strategy

The final step is to create the strategy using the information inserted in the previous steps. This consists of creating combinations of acceptable objectives. Based on preference, the user can group objectives to create a list of objectives that are used to measure the success. This will create the strategy. Added to that is text describing the allowed risk as well as any known information about the market, such as competitors developing, special circumstances for the compound etc.

Define actions

With the objectives and the compound added, it is known what information needs to be researched.

Creating the action list

The need to known information can be expressed as compound aspects that need be researched. These aspects are then compared to outputs of actions to select the necessary actions. Summing up these actions creates the action list. Actions include studies, analyses, decisions, meetings, regulatory communications and custom.

Design actions

The action list contains actions that were added in their standard form. These often need to be customized, which is done in this step. Information included here is: standard duration, cost, output information parameters, phase in which it is performed and dependencies.
These can all be customized, as well as the quality requirements: non/GLP, organization performing it.

Creating scenarios

This step uses the actions and the objectives to create scenarios, the outputs from the actions (those expressed in parameters), are used to create the scenario space and options. Using the actions and the objectives, parameters for scenarios can be identified (step 1). Setting levels for these allows the creation of scenario. In this case, scenarios are always linked to an action, which is the first action since all the information to verify that the scenario will be as it will be is possible.

Plan actions

All the actions currently needed can be planned in time is this phase of design. The actions have been designed in the find studies step, for the duration and effects they produce, in this step they are given a start date, (end date will be filled automatically). Additional properties can be assigned to actions here, including critical path, start and end dependency. Actions can be dragged from the action list to increase ease of use, which is further increased by time, risk and budget optimization functions.
5.1.2 The control section

The control section is the section used to gain overview of the project status. It provides the information to the project team, showing project actions, progress and most important, the information available.

This is done with the same general interface as presented in 5.1, using the category and action column. The action screens are different from the design section, most do not allow direct interaction (this is done in the design section) but present information. Some action screens require decisions to be made, these decisions were designed in the design section.

Categories in this section are:

![Kinesis Project Control](image)

**Figure 5.4 Kinesis project control overview section**

**Project overview**

The project overview has four actions, each gives information on the status of the project.

**Project status**

Project status shows the planned actions in time. Each action is represented in the timeline with the project and compound results. These are represented as the six rectangles underneath an action, showing green if the project cost, quality and time are within boundaries. The line below shows the same for the compound
information. Both lines are tested along design specifications of the action or objectives of the project.

Project Breakdown

This is mainly project information, showing the interaction between cost, time and quality. It will also show how this information was created.

Decisions

Decisions show all the decisions in the project, past or present. Upcoming decisions are presented with the information they require, scenarios and options available per decision. Made decisions are shown when they were made, what information was used and a description why the decision was taken. This screen also allows certain decisions to be made, inserting the decision outcomes directly into the project without having to go to the (re)design feature.

Study summaries

The study summaries are an important source for interdepartmental information. With this feature, the project member can review if new studies and analyses are finished and how the information affects actions in his department. There is an action here to add summaries to the project.

Compound information

Compound information shows everything about the compound performance.
Compound information

This shows all the information available on the compound, including name, mechanism of action, the known information measured to the (compound) objectives.

Drug Product

Shows the information on the product, which is the compound, formulation and administration. Also information about use and container packaging is presented.

Production information

This section presents the information about the production of the compound. This includes production time and cost, as well as what actions will be performed to increase production and how this affects previous and upcoming studies.

Competitor products

This section shows if there are competitor products on the market and if so, what the profile of that product is in terms of this projects objectives. Actions here include adding these competitor products.

Clinical condition information
The clinical condition information requires actions before it can yield information. This is to make the decisions on clinical condition and indications. Once these are made, the information about this field of the project will be provided by presenting current treatments (as far as known by the system), mechanism of action and effects that influence safety and efficacy performance, it also sets boundaries (for example, if a clinical condition has the symptom of belly flux, oral administrations are not an option).

Actions here include the setting of the clinical condition and indication. Multiple clinical conditions (and indications) can be set for a compound.

Figure 5.6 Kinesis project control clinical condition information.

Project team

The project team category allows communication in the project, such as requesting information and sending it, as well as planning meetings etc.

Reports

This section allows access to all the complete reports in the project. This is needed when a summary does not give sufficient information. Actions here include the adding of reports, which can be linked to actions.
5.2 System development

Developing the software system is the system development phase of systems engineering [Sage, 2000]. The system definition was used to interpret the pharmaceutical development setting, which has given requirements for the system. The next step in Systems Engineering is the system development which, in this case, transforms the found system into a software design.

How this transformation should be done is not described in the systems engineering discipline, so a method to transform the requirements into the software design is needed. Systems for decision support are best designed with the user specifications first [Turban, 2005], stating that the top down approach, starting at the end user and finishing at the computing requirements is preferable. From the many different methods of software design available, the method of Munson [Munson, 2006] fits best in the settings of decision support and systems engineering.

Munson describes the process of designing software as Requirement Engineering, a three step process. This consists of creating operations, defining function and creating modules.

Creating operations

Stating what the user does in his normal workflow, is the basis for defining operations. Operations show what kind of actions the system supports and is based on the combination of issues and workflows of pharmaceutical project management. For this, the conclusions from chapter 2 to 4 are used to describe the actions the project team performs during a project.

Defining functions

The next step is the functional specification, the functions a computer must be able to perform to enabling the users to execute their operations. This is a translation of the user’s operations into actions the computer must perform.

Creating modules

The last step is to group the functions into modules, a module is a group of functions that enable (a limited) amount of operations to be added to the system. The use of modules has the advantage that it allows for easier development management.

In this thesis, the scope extends to the middle of the functional level, where it can be stated whether the described system will be programmable. This fits with the research question to investigate whether the development projects can be supported.

5.2.1 Creating operations

Creating the operations is a three step process. The first step is to state the operational system overview which is, in essence, an executive summary of the user’s operational system, the action a user performs. These actions must then be described to be supported by the system.
The actions a user does depends on his role in the project, so for each role the actions have to be described. Using the roles from 3.2.2, there are three categories of users: project leader, department representative, sponsor’s representative. Actions are also dependent on whether it is a design or control environment, a difference that was presented in 3.3.1. The design actions are described by role, followed by the control actions by role.

**Design**

There are two different roles that design, the first is the project leader, who designs the overall project, the second are the department representatives, who design actions.

**Project Leader**

**Create a project team**

To run the project, a project team is needed. The project leader’s first task it to create and fill the roles needed in the project. This is done by defining the project expertise need, translate that into roles and then assign human resources to fill these roles.

**Create a project strategy**

Creating the strategy is the task of the project leader. Using information and expertise from the whole project team, the project leader first creates the objectives and then formulates the strategy for the project.

**Creating the project plan:**

*Defining project actions*

With this step, the project leader creates the action list, all actions to be taken in the project. Information needed for this is the result of offline meetings, the results of which have to be inserted to create the action list.

*Planning actions*

The project leader plans the designed actions in a project time line. These are set into the path, taking dependency, critical path and preferences into account. Again, the path is decided offline, while the results are inserted into the system.

**Department representatives**

**Create a project strategy**

The role of the department representative is to provide information to create the strategy. This consists of information on the compound, expected results and guidelines relevant to the project. The department representatives present and place this information at an easy accessible location for the project team to use this information.
Creating the project plan

Designing actions

In this step the department representative has to design studies, setting the specific requirements that the development requires. This includes factors such as outputs, duration and start time.

Sponsor’s representative

Create a project strategy

The sponsor’s representative task is to provide the preferences of the sponsor. This helps create the setting for the objectives. Adding information on budget, time and risk information will help create the strategy.

<table>
<thead>
<tr>
<th>Project Leader</th>
<th>Department representative</th>
<th>Sponsor’s representative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Create strategy</td>
<td>Create strategy</td>
<td>Create strategy</td>
</tr>
<tr>
<td>Set objectives</td>
<td>supply information</td>
<td>supply information</td>
</tr>
<tr>
<td>Select objectives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Define project actions</td>
<td>Define project actions</td>
<td></td>
</tr>
<tr>
<td>Find actions</td>
<td>Design project actions</td>
<td></td>
</tr>
<tr>
<td>Use all info to plan action</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5.1 Project members in project tasks

The project leader has two tasks in the control of a project, communicating and decision making.

Knowing the project status

The project leader uses the system to gain insight in the project status, retrieving information on the project actions and comparing those with the planned project path. Using objective information categories, the project leader will be able to cost, time, results and quality of the project at the current time.

Decision making

Decision making is done by using the information needed to select the options and then select one of the futures presented by the scenarios. If no suitable future is presented, this can mean the project should be either redesigned or terminated.
Communicating

The project leader uses the information in the system to create external data, data for the sponsor’s representative to review. This consists of both project and compound information in order to present full insight into the status of the project.

Redesigning the project

In cases a partial or full redesign of the project is required, the project leader can do this in the design section of the system. During this redesign, the information needed is presented just as it would be during the control phase, except that the project leader can alter objectives, future actions and scenarios.

Reviewing old decisions

These decisions are modeled in the system, presenting the used information and assumptions for the project leader to verify the decisions. The project leader’s task is to model the outcome of the decision in the system, as well as verify that the information used to make the decision is present in the system.

Department representative

Decision making

Decision making for the department representative consists of presenting the relevant information for the decision. In the system, this translates into uploading the relevant information and linking it to the decision.

Updating the information

The department representatives are the connection with the external organizations such as CRO’s and SSC’s. They are the ones that receive the information about the actions performed at that organization and will have to share this with the project team. This is done by inserting this information into the actions in the system and adding the outcomes as well.

Decisions are made on results and assumptions, results can be expressed in parameters, this is not always the case with assumptions.

Criteria for decisions are often a mix of multiple pieces of information, the weight of this information is subjective to the decision maker. Like objectives, there are multiple combinations of parameter results and assumptions possible to meet the criteria. As the situation changes, the optimal decision may alter. Being able to recall all the information and assumptions from the time a decision was made will help to check whether they are still valid and if they are made for the right reasons.
Managing time and budget is done on a different level than deciding the actions to perform in a project, but those actions are always taken with time and budget in mind. The compound information is the navigating information, others pieces of information are used as boundaries. In order to manage the development strategy, these factors need to be presented at their level of detail, which is different between budget and time on the one hand and compound information on the other.

In any project, the following sub goals have to be achieved, these are decisions which need criteria set:

**The communications of status**

Communication is needed for project team internal and external use. The internal use is needed to show new results have been found so the project team can stay up to date. Reports, summaries and the updates of the IB\(^{11}\) and project plan are made available to the project team. The system should transform the current storage of information from a cold medium to a hot medium. The transformation helps to solve issues about showing the interaction between studies and project planning by supplying mission critical information, thus making information available at any time. The transformation will give and giving uniform information to all project members involved.

External information has three different aspects:

Studies and analysis, as well as other actions\(^{12}\) are performed by external companies. They will inform the project team of their needs and boundaries, the information needed to perform their actions.

Regulatory control demands formal reports with specific information. These reports are made according to formal regulations, some of which can be supported by the Send methodology [Papoain, 2004].

An RO will need to communicate the status of the project to a sponsor, a VC or higher management. This requires the function to present the project status and inform of decisions. Based on the analysis, the communications should show the current status of the project and what the next decisions and options are. A preview available options and what effects this will have on the project will generate the strategic level of overview required.

**Translation to operations**

In the previous section, a description was given of the actions users perform when using the system. Using Munson’s method [Munson, 2006], the next step is to change the actions into operations. Operations are the steps a user performs in a software program to execute the action.

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\(^{11}\) Investigator’s Brochure, the document containing all the compound information about the compound.

\(^{12}\) Such as writing specific reports for regulatory organizations
When creating the roles, the user selects standard roles from the system. For the user this means to open the database and select the roles he wants. For the system this means to open the database at the right time and present the roles.

To set up come to operations, one must visualize what a user does in order to perform that action. This is a subjective process, as each person has a different visualization of how the actions are performed and how this should be supported [Zhu, 2005].

**Operational animation**

The last step of setting the system requirements is to introduce the operations that animate the model. The operational animation steps are the operations that allow changes in the system, caused by the users.

Animation as presented by Munson is the method of presenting the software system to the user. In the case of the operational animation, it focuses on the operations a user has to do not due to using the system, not due to his requirements. In essence it points to how the user can navigate through the system and how he can change data and models. The user is required to perform navigational operations, such as going to different areas in the system. While these areas are a result of operational system overview, the operation of moving with the system is not. As ease of use has become an ever increasing requirement in software [Munson, 2006], this should be incorporated early in the development.

The changes and updates can be inserted two ways, the first is the operational way, i.e. by users, the second is the functional way by the computer. Both update methods are shown and explained below.

As was shown, many redesign options, as well as decisions and criteria cannot be set at the beginning of a project and need to be filled in later. In the operations list, a chronologic order to the actions is applied, due to dependencies based on requirements. This order is not fixed, in case of redesign, it is possible to start in the middle of the project creation steps.

Navigating through the system should be very similar to the current way information and actions are performed. This means that the system should emulate the current information storage and action sequence used in projects. These are currently divided by project management information and compound information. This distinction should be present in the system as well. The project information is further presented in its three project factors, which should be available at the same time to enable good overview of the project status. Compound information is a bit more complicated, as there are different ways it is stored. The first is the IB, which can be emulated by a data sheet of all relevant information of a compound, an executive summary. The second way compound information is stored is by department. This is mostly done as source data summaries on specific topics. Both these types of information storage should be present, as each has its use in the current methodology.

The separation of project information and compound information is needed in the current system, but it is also the cause of one of the issues. This is the issue of giving an overview of the effects of
study results on the project. A new option of overview should be created, which shows the studies, their possible effects on the project plan and what actions can be taken. This is a currently unavailable option in any of the support software. This is an area where the operational animation and functional animation will meet, changes in this overview will be operational and functional. Operational changes will be in the form of inserting decisions and changing the project plan. Functional changes can be the results of preprogrammed functions (such as updating the date) or second generation operational changes, changes inserted by a user elsewhere in the system that will be forwarded to this overview.

This step is important not just for the final result, but is used during the specification phase to enable mock up model testing. It will enable the actual users to get a feeling for the software and imagine how they will use it. With this knowledge, they can provide feedback to the requirements engineer.

5.2.2 Defining functions

Functions are the tasks a computer performs to enable the user to use the software. As with operations, the creation of functions is a gradual process of transforming the source information, in this case the operations, into the final result, the functions. In this phase, functions need to be expressed at the level of code, but their use should be clear.

Mentioned earlier, the step of transforming operations into functions is outside the scope of the thesis. Because there is currently no system that performs the required service, the possibility could arise that computer are not equipped to manage projects like these.

Information management

With the advent of the computer, the pharmaceutical industry has undergone a change in communication. Due to the large volume of data, the pharmaceutical industry soon switched to digital media to communicate this data. All information is managed digitally\(^\text{13}\), though some official documents are still signed on paper.

The information management is not considerably complicated. The current system of storing information is simple but adequate. Project management information is already being managed in software like MS project, data storage for raw data can be done with any of the numerous archive systems. No comparable tool was found for a complete overview of the compound information and one in which actions and scenarios were presented in a clear way.

Creating a compound information summary module should be possible. The IB serves as a blueprint for required format and from the system the inserted parameters can be used to insert data into this format.

\(^{13}\text{As stated by Kinesis drug development teams and departments members}\)
The scenarios overview is something that is possible with current technology as well. Being able to create a visualization of the actions to be performed, with the different option has become feasible.

Supporting the decision parameters will be more complicated. Each project has unique parameters, so it will be impossible to pre generate them all for a project. What will be needed is a system that allows the project team to build their own parameters. This is going to be a complicated task that should be carried out for every project. Fortunately, this step is already performed “offline”, so the requirements of what should be supported can be found. As described in chapter 3.3 about parameters, these will always consist of a name, a value and a unit. Having a system in place that will allow the project team to create these parameters, the criteria can be built up like Lego. Some parameters can be standardized as they will be used in many projects, so a kind of parameter library would speed up this process.

Modeling decision is possible as well, not just the effects of changing direction in a project can be shown, but the internal working of a decision can be shown as well. The parameter combinations can easily be imported to a decision, not only taking the name, unit and value, but being able to gather these parameters from multiple studies. The criteria can also add assumptions, which are statements about what is expected to happen. These can be validated on a later date, which allows the computer to track whether the decisions have changed due to increased knowledge. The computer system itself can perform preliminary comparisons to check whether the outcomes fall within the criteria and, dependent on the predefined actions available to the project team, can even hint at the next steps.

Communication of some of the information will be difficult. As there is no good way to divide information based on level of detail, the communication of project status would only be possible by using the project overview mentioned earlier. For some actions this will too limited. For communication information to a VC, an executive summary of the project and the compound would be preferable, to give the VC access to the system (from a RO point of view)

Using the system to actually make decision is not possible either, it will only show what was deemed important at the time of design, what the outcome of the found information is and what actions are available. There is currently no method to actually manage meetings.

Most of the operations described above seem possible to be created. There are some new, and to the industry unique requirements compared to current software, but this does not seem to be a large obstacle.

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14 As stated by Kinesis project leaders
5.3 Validation

Validation methods are based on the methods described in the Building software and Software design Methodology books. For balanced validation, it is important to focus on validating the following steps of the system:

- The description of the environment
- The description of the actions the environment performs
- The description of the actions the users perform
- The translation of actions into operations
- The translation of operations into functions

The first two items were validated by a sequential version of the Delphi method, the description of the environment and the effects the environment has on the project (as described in chapter 2) were presented to the different project experts. A first version was presented to each of the experts and was asked for feedback on correctness. With this feedback a new version was made which was used in a similar way. This second version did not require any changes to be accepted by the experts.

The description of actions performed by the users was reviewed with the department representatives and the project leaders. A description - excerpts from chapter 2 and 3 - of the actions, was presented to request feedback. With reference to this feedback, minor changes have been made, but none required significant redesign of the actions to warrant a second round of changes.

The translations to operations are validated in a similar fashion to the user actions. First the actions were presented and the resulting actions in the system were described. Acceptance was measured with a questionnaire of twenty questions asking feedback on the match has to actual actions, the completeness and a score was asked to be given for the method of use. The grading did not receive any score lower than a 6. The two cases which received a 6 were from different members, in both cases in areas of their expertise. After rephrasing of these operations, a 7 or higher were given, which was the minimum standard.

The validation of functions was not done, the goal of the creation of functions was not testing whether they represent the system accurately (as is the goal when building software), but to investigate if the required functions would be possible to program as this is the main goal of this research. An independent software developer was asked for his opinion on ability to program these functions. In his reply he stated that it is complex, but possible.
Validation methods

Validating the system shows the correctness of the research. This step should be done seriously and according to official methods, consequently interested parties will accept not just the validation, but the system itself. The targeted groups for validation are users and the experts that have given the information to describe the system. With their help, the made analysis, summaries and operations can be checked using an expert system, to validate parts on which their expertise runs high, as well as general material that will validate if the general setting is correct. For this validation, the departments heads of Kinesis were kind enough to contribute their expertise.

<table>
<thead>
<tr>
<th>System name</th>
<th>External network</th>
<th>External constraints</th>
<th>Project structure</th>
<th>Information need</th>
<th>Information structure</th>
<th>Internal network</th>
<th>Decision making process</th>
<th>Strategy management</th>
<th>Total:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thesis</td>
<td>---</td>
<td>+</td>
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<td>45% / 9</td>
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</tbody>
</table>

Table 5.2 Measuring the proposed system

For the external network, a mixed score was given. While the system could easily provide insight to external actors such as the VC, there is currently no dedicated section to support communications with any of the other actors.

Modeling external constraints was considered to be done using the effects these actions have on the action plan and information need. However, designing them is only done indirectly, which makes tracking them difficult.

Designing the project using the standardized actions is supported by the system, it will not only be able to provide the actions, but the customization will be able to add requirements and project specific aspects to any action planned this way.

The information need is mainly supported by the setting of objectives and criteria. This will enable all information needs to be mapped, but there is as of yet no direct way to support the new insights gained during the project, these will have to be updated manually.

The information structure is supported by a database that is able to manage and track the data and information of all kinds using meta data to provide it at the right time.

The use of roles is used to model the project members and give rights and information preference to members. The open access to any information support the information need.

The decision making process is mainly done offline, and as such can only be supported by planning the decisions, providing information and tracking the outcomes. While this is in the goal of the system, there are different tools that support the decision making process better.

The screenshot above show the complete adaptability of the strategy by using objectives to track the strategy. These can be set at the start and be altered during the project, which is essential for the
project. However, the methods of changing are done directly at the design interface, which would require a redesign decision to be made at every change in the project, which is not as close a support as would be optimal, there are no links between the actual outcomes that have required the change and the changes made. This is something that will have to be improved.

5.4 How to start the development process

In this section, a short analysis of how to start the development process is made. This will consist of weighing two factors, the need of the supported aspect and the viability of building it.

The needs

Of the eight specific features of drug development projects, the feature of strategy management is the most important. This is because there is currently no support available for this feature, yet strategy management is at the core of the project. A second important aspect of development projects that is not supported is the decision making process. The decision making is unique and at the centre of drug development, yet there is no support for available. The different network aspects (internal and external) are special in the way they are configured, but the features are not as unique as the previously mentioned aspects. Most of the network requirements can be filled by current software systems, so it would not be advisable to use this feature as a basis for a new piece of software. The information need and structure are unique however, and there is a need to manage this. The information need and the strategy are closely related, though the information need is on a more operational level. It is therefore suggested that in order to start support, this aspect of the system is developed first.

The start

Starting with the information structure will allow to create a good foundation for the rest of the features. Not only will the information categories be supported to identify the information needs, also the formal/informal and internal/external aspects of information can be modeled, which enable the network environment to be supported. As it seems likely that the network aspect of the system will have a larger impact on the software aspect (requires internet support and different roles and functions), it would seem a good approach to develop this structural part first. However, the danger of developing a network system that will not be able to help guard the development strategy is present. Software development is an industry that is very susceptible to path dependency and lock in effects (Zhu, 2005), which would make the approach of going for the information structure first and the strategy management module second a safe bet.

Starting with the information structure module to track all information, the next steps should be the information need. With this, the use of the information structure if amplified, while adding relatively little new functionality. After this, the decision making process should be added. This will enable a full project planning support, even though the methods of coming to this project plan are not yet supported. Next the external factors should be implemented as a step to be able to support the
strategy management module. Once the strategy management module is in place, it can use the external factors and information structure to model the objectives and goals. This will help fill in the information needs, which was an offline step until now. Last feature to be added is the network support. This should start with the internal network, as this will help provide information to the project member that needs it and reducing the information overload for other project members. Another benefit from going for the internal network first is that the developer can practice on the internal network, which is a safe and open environment. Once the network support is functional, a more hostile environment can be approached, which is the external network.
6 Conclusions and recommendations

The research for the thesis was started to find an answer to the question:

“Can the project methodology of Kinesis Pharma be supported by a tool that will help to guard project strategy, project viability and information quality?”

In order to answer this question, two questions each with sub questions, about drug development projects need to be answered:

1. How does Kinesis Pharma approach drug development?
   a. What are the general settings for drug development projects?
   b. How are projects run and how are evaluations done?

2. Can the Kinesis Pharma approach be supported by an information system?
   a. What are the requirements the industry, the projects and Kinesis might demand from such a system?
   b. What functionality can such an information system provide?
   c. Is there a match between the required functionality and the functionality that is possible to be provided?

The conclusions will start with the lowest level questions and will be concluded by answering the main question.

1a. What are the general settings for drug development projects?

Projects are notable for the complexity and high amount of information that is needed to develop a drug. This requires a team of experts in different fields of science to design and track the project.

Each of these experts is the representative of a department that does different aspects of the development, which are needed simultaneously to develop a compound. The team setting causes information and knowledge availability to be fragmented in different areas of expertise. Sharing information is further complicated by the uncertainty of the information need. Different members supply and require specific information, but the exact supply and demand is not always known to the team members.

Outside the project team, there is an external network of actors that can influence the project as well. This network has information needs which is different for every actor. The external network has
specific influences on the project per actor, ranging from an operational action level to the setting of strategic objectives.

The projects are influenced by many factors that affect the options available during development. These influences often cause changes in the project, which then needs to be redesigned. During the designing of a project, the team is also limited in their design options, most notable is the project template, which causes all projects to be run in phases with specified research goals.

*It can be concluded that projects in drug development have a different setting than projects in other industries. This is caused by the dual network setting, the diffuse information management, the unique project template and the high flexibility in projects.*

**1b. How are projects run and how are evaluations done?**

Controlling the project is done by the project team, a group whose configuration is dictated by the information need. This team analyzes the compound’s results to decide how to continue the development. This is done as a group, each member needs to be present to provide information and expertise during decisions. On lesser topics, individual project members can make decisions and designs. Decisions are complex, but highly structured and there is limited variability in the decisions.

All development projects have the same general goal, to develop a compound. Using information and expertise based on pharmaceutical and chemistry knowledge, the projects are designed and steered, after which the “standard” project management techniques are applied by the project leadership to manage and optimize the project. Setting the compound objectives is done by the whole project team, due to the complexity of the projects the expertise of multiple development areas is needed. Setting the optimization objectives for the overall project is mainly done by the compound owner.

Controlling the changes in projects requires special attention. First the scope the of the change needs to be determined after which the project team, or part of it, needs to adjust the settings of the project. These changes can alter objectives and criteria in such a way that future and past decisions are no longer valid, each of the changed decisions is checked to verify validity and adjusted if required.

To measure the success of a development, the success of the compound and the success of the project are measured, which is different from projects in other industries. It should be noted that managing and steering both affect the project success, but steering will not affect the project execution, nor will managing affect the compound success. The factors used to evaluate project management success are the same in every project. These factors can be used at every level of the project. The compound and project information is measured in a standardized set of categories, though the way to measure these categories differ per project.

*Conclusion from the running and evaluation of projects in the pharmaceutical industry is that both the control and measuring the success of a project are complex, but structured processes. The steering is done as a group effort, while the managing lies more in the realm of the project manager. The decisions have the power to change the project.*
2a. What are the requirements the industry, the projects and Kinesis Pharma might demand from such a system?

The requirements set to an support system can be divided into two categories, the “standard” project management support and the Pharma project support.

The standard project management support requires the tracking of action and the ability to create a clear project overview. This requires the tracking of the “standard” project management parameters.

The Pharma project management has distinct factors that affect the support requirements, which set the following requirements:

- The system should be network compatible; the different kinds of information supplied to the internal and external actors must be differentiated and supported. The interactions that occur when making the design and running the project are important for the project design and therefore must be modeled.
- The system must be able to present the constraints set by external factors and regulations by expressing the effect they have on the project.
- The project overview and design has to be able to present and make use of the phased system, the sub-goals and the information requirements set by the project template.
- Creating support does not change the way information is created or gathered, which means that the system must be able to manage diffuse and fragmented information sources, while being able to present a clear picture to the project team.
- Decisions use large amounts of changing information and are decided on a number of criteria and parameters. The parameters and criteria are found in different information departments, but have to be combined to make the decision.
- The strategy management aspect requires flexibility in the objectives, criteria and parameters that are used to measure the success of the project. These affect the information need and can thereby change the whole project. It is therefore needed to be able to track how the measurement system is related to the actions in the project.

2b. What functionality can such an information system provide?

The “standard” project management aspects have been supported by numerous programs which are up to the task of supporting these aspects. This includes time and budget overviews, as well as Gantt charts, team communication and planning of actions. It can therefore be concluded that this aspect can supported for projects.

The Pharma project support managed can be done as presented below:

- The external network setting can be supported by created asynchronous communication facilities. This is easily done by using internet accessibility as a basis for communication. This
will not only allow the unique communication to be designed for the individual actors, but can also be used as an archive system to track the communications. Any constraints set by an actor can be modeled as external factors.

- External factors can be modeled in different methods, dependent on the need. Some will be affecting how the projects design interface works by adding dependencies between actions, others set constraints when creating objectives and criteria.

- The project structure can be supported by creating a project design interface in which actions are created or selected and then placed on the project path. Using linking, these actions can be stringed into a project plan in which actions, scenarios and decisions can be modeled. The individual phase goals can be modeled using the same method as the project objectives.

- Modeling information needs to be done while keeping the information structure, consisting of the content, level of detail and source, intact. The fragmentation of information is easy to manage of a database structure, so it is possible to create a system that makes the information logically and easily accessible to all project members.

- To support decisions, these must be represented by the system. Using the database, the information needed for the decisions can not only be provided, but it can also distinguish between the most recent version of the information and older versions. Depending on the need, information used earlier decisions can be presented along with the new values of the information to verify decisions.

- To support strategy management, the system is able to link the objectives, criteria and parameters throughout the whole project. This means that if any changes are made, it will be possible to see what actions, decisions, objectives and strategies are affected by these changes. More complex version can even determine if these changes are within particular ranges and then prioritizing the attention accordingly.

2c. Is there a match between the required functionality and the functionality that is possible to be provided?

Using a computerized support system enable the Pharma specific project aspects to be modeled. Considering the main goal of the system is to track the development, modeling helps in guarding the development of a drug. A computerized system can provide additional support however, it can organize information, present it at times when needed and allows changes during the project to be managed more easily.

*Question 2c. can be answered positive, there is a match between the required and provided functionality.*
**Final conclusion**

Drug development projects are different from projects in many other industries. The diffuse information, the networks setting and the high flexibility set these projects apart from other projects in other industries.

Support for drug development is needed, issues with sharing information, decision making, gaining insight in the project status and strategy management can all be related to the complexity of the projects content and structure. Current technological progress will keep increasing this complexity, while none of this progress is applied to resolving the issues.

The project management methodology is formalized and structured in such a way that it is possible to determine and design the support needed for the unique environment. An analysis of this support need has shown that the possibilities of the current technology are sufficient to create this support in the form required by the industry. With this knowledge, the final conclusion of the research can be drawn:

*It is the conclusion of this research that it is possible to apply the current technology to support the project methodology of Kinesis with a system that helps guard the project strategy, the project viability and the information quality.*

Many projects in other industries do not require this level of complexity. Of main importance are the difference between the content and project control, the setting of multiple ways of reaching a goal and the project redesign during a project. Project like this are definitely not the standard, but other field of industry were found in which have some similar characteristics. Most of these fields concern development of some kind, marked by high degrees of freedom in design and heavy need of expertise, as encountered in any design environment such as vehicle or software design. Industries with a distinct difference in information content and execution could benefit from this system as well, such as for oil drilling. An important factor seems to be that the execution setting is in a project management style, for example, politics have high degrees of freedom and a distinct difference between content and execution, but this system would not seem to add any use.

**Recommendations**

With both the need and the opportunity for creating the system shown, the first recommendation is to actually build such a system. For this, the information in this thesis is a good basis, but more is needed to be researched to gain a complete understanding of drug development projects. Topics such as group decision support, the risk management and the guideline transformation to constraints and objectives were all left out the thesis due to time constraints, but will add to the use of the system. Also in the current research, the analyses were focused on the scientific aspect of the research and paid less attention to the economic and regulatory aspects. Project members such as the marketing departments were left out, but they have influence on the project management and information supply that were until now considered to be external constraints. It is recommended that additional research is done to find the requirements this project member requires.
7 Reflection

Writing a Master thesis is about applying the skills and techniques learned during the course of the education. My thesis research at Kinesis showed me that the three pillars of my master’s program, System Engineering, Policy Analysis and Management (SEPAM), are clearly represented, which allowed the application of many of the skills learned during the education.

The Systems Engineering approach has made it possible to structure the project in a way that is practical in approach and is easy to apply. The use of situation assessment, finding relations and validation methods are all directly related to the Systems Engineering methodology and have helped to gain understanding of the system. In the same way, the decisions are able to be modeled quite literally using Systems Engineering approach. However, early in the project, it became apparent that the Systems Engineering approach would not be able to assist with some of the problems caused by distinct properties of the project. In some areas Systems Engineering does not fit well with the project’s aspects; mainly in two areas of importance, the setting of the goals and the translation into software requirements. Using the Systems Engineering approach for goal setting would have required to set a clear and measurable goal, which in drug development proved to be impracticable. This problem was solved by using a slightly different definition which does still fit in the Systems Engineering approach. The second situation is describing software system requirements. While the Systems Engineering approach is able to clearly define the drug development projects, it does not help with the transformation of these definitions into a set of software requirements. Systems engineering does not provide any method to do so, even though most systems developed nowadays are computer related.

The SEPAM curriculum helped to create insight in most of the fields needed, such as network management, project management and information structuring. The research required additional fields, of which some were new, such as basic pharmacology, chemistry and biology understanding, and of course software development.

To carry out a project which was until now completely undefined has been an interesting experience. One of the more interesting aspects amongst others has been the freedom to define needs and to analyze the requirements and how to work with that. Due to the large amount of data available, it was sometimes difficult to separate the information from the data. Fortunately this became easier as systems engineering was applied to all the information. This lessened the abstract nature of many of the topics and made it possible to decide and elaborate on the aspects that needed to be described for the system. Processes of this nature favor the top down approach, starting with determining the needs and requirements and then finding the information to fulfill this need. However, much of the information gathering was done bottom up. This approach can be attributed to the new topics. Without the basic knowledge, it was impossible to determine what was important.
References

AR: American Research, Investments in global health research, 2006
Found 08-07-2008

Aschman, Allison, Paper on project management research for the pharmacological industry:
http://www.ipaglobal.com/inside%20pages/Ind_Areas/Pharms/ipa_pharms_prospectus_2006_summary.pdf,
found 08-01-2008.

Berrogi, Giampiero: Decision modeling in policy management: An introduction to the analytic

Beirly, Paul, A. Chakrabarti: Generic Knowledge Strategies in the U.S. Pharmaceutical Industry;
Strategic Management Journal, Vol. 17, Special Issue: Knowledge and the Firm, pp 123 - 135

de Bruijn, Hans. A., E.F. ten Heuvelhof: Management in netwerken; Utrecht, 1999


Evens, R.P: Drug and Biological Development, Jacksonville, 2007

FDA:, Challenge and opportunity on the critical path to new medical products,
http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html
Found 08-01-2008

Groen, Kees: The X-factor in drug development, presentation at the ten year anniversary of Kinesis.
Rotterdam, 2007

IMS Health; Global Sales 2007; 08-07-2008
http://www.imshealth.com/web/content/0,3148,64576068_63872702_70260998_83746585,00.html
found 06-03-2008

Krishnamurthy, Nikhilesh, A. Saran: Building Software: A practitioner’s guide, New York 2007,

Meredith, Jack r., S.J. Mantel: Project management: A managerial approach, Hoboken, 2006,


Priti, Kumar: Presentation on the future of development, held December 2006 for Pfizer international
Used Google search term: “annual drug revenues”, Found 08-01-2008 Link to .ppt file currently not found.

Sage, Andrew p., J.E. Armstrong jr.: , Introduction to systems engineering, New York, 2000


Turban, Efraim, J.A. Aronson, T. Liang, R. Sharda, Decision Support and Business Intelligence Systems,


Papoain, Thomas; 2004, Update on SEND. www.fda.gov/cder/regulatory/ersr/papoian.ppt
Found 08-01-2008

Zhu, Hong, Software Design Methodology: From principles to Architectural styles, Burlington, 2005,
Appendix A: Analysis of Drug development actor network

Drug development forms a spider web within the pharmaceutical industry. There are very few organizations from outside this industry present or needed to develop a drug, but within the industry there are very few organizations that are not involved directly or indirectly. Within drug development, almost all companies need expertise in some form or another from one or many other companies. The six different organization types listed previously give a good indication of what type of actors can be encountered during a development project. In many cases, more than one company of each type is encountered in a project. Depending on the size of a company, these different organization types can be integrated into one organizational structure.

Each of these different organizations will be asked by the research organization to help in the development. Each company has their own approach to their part of the project [de Bruijn, 1999], but they will share the same general goal as the contracting company. Their own agenda might influence the project in ways that need tracking in order to find the status of a project.

Research organizations (RO)

The research organization is the organization developing a compound. This is the main actor during a research project. For Kinesis, this organization would take the form of a sponsor hiring Kinesis for support activities. A research organization is thus named because they drive the research, though this does not mean the organization does any of the actual research itself. It is the coordinator for the development of a compound and manages progress. It is this actor that finds the funds to run the project and sets the objectives for a compound. Important skills needed in these organizations are the ability to oversee all the requirements set to a compounds development, and to see to it that these requirements are fulfilled.

The research organization usually has only one goal: To develop a drug as long as this is a potential success. Success can often be interpreted as economical, though there are organizations that perform research purely for the scientific gratification or to create a medicine because they feel it should be available.

While most large drug companies have targets for success rates and for creating a certain number of highly successful drugs, block busters, over a period of time. Smaller companies are usually forced to have less ambitious goals. Classically the main goal was to fully develop their own compound, though lately a variation on this goal has gained popularity. A successful project is no longer defined as bringing a drug on the consumer market, the pre consumer market is now a valid target as well. Successfully selling a compound in development to another company, having one’s company being bought by a larger organization or even just holding patents for certain compounds are now development strategies that can be a success as well. These different goals have their impact on the development strategy, there are four generic knowledge strategy types [Bierly, 1996] to be identified in the industry, the ‘explorers’, the ‘exploiters’, the ‘loners’ and the ‘innovators’. Each will set the
objectives, boundaries and scope of knowledge management, risk and development speed differently. This is an important aspect of the development strategy. The explorers are looking for new and unconventional compounds, expanding the boundary of pharmaceutics. Exploiters tend to focus on what they already have and how they can keep that in the market. The loners try to keep as much of the development in house. Innovators try to use existing compounds and improve them or find new uses for them. The objectives of the organization doing the development have to be set clearly in order to allow the creation of an appropriate development strategy.

Depending on the size of the research organization, many of the types of organizations identified at the beginning of this chapter can be incorporated into the research organization. In this case, it is an inter-organizational network [de Bruijn, 1999], which is governed by different mechanisms than an intra-organizational network: The internal network consists of the divisions based on expertise and industry knowledge on the one hand, and the corporate and business requirements on the other hand. The external network will consist of (dependent on size again) various other organizations they require. No matter how large a company, there will always be an external network, for example regulatory control will always remain an external actor.

**Venture Capitalists**

Venture capitalist companies (VCs) assist drug development by providing funding. Most of these companies are looking for economical return on investment worth the risk in funds and time. The pharmaceutical industry is an attractive industry for them, as returns can be very high, while the mean of the industry investments has only slightly more returns than overall cost [Evens, 2007]. When investing, the VCs will want to be kept informed on their investment. Very often the investing organization also requires some control over the project they are investing in, which may interfere with the development strategy set by the companies. Usually interested in the purely economical returns, development and goals might look very different when pressured by a venture capitalist company.

The power and control of a venture capitalist varies per project. This is influenced by dependency on the VC and their capital, the size and profile of the project and even the strength of character of the VC and the project leaders [de Bruijn, 1999]. As the industry is funded for a large part by venture capital, there is often little trouble finding diverse sources of funding, therefore, there will initially be little dependency on one VC. As a project progresses the dependency on the VC grows with the investment, usually increasing their control over the project. Because of the huge amounts of capital needed, the withdrawal of capital of a sponsor will slow down or even halt a project until new funding can be found.

**Clinical Research Organizations**

Clinical Research Organizations (CRO’s) are highly specialized laboratories and test centers that do the research required to develop a compound. These are the organizations that do the actual pharmaceutical testing. Once submitted to a CRO, the compound will be tested according to the
specifications given by the compound owner. They test the compound on different parameters and submit data back to the research organization as raw data. Very little can be said about the effects a compound has based on this raw data. Most early clinical research organizations will therefore also present reports with a limited analysis of the findings. As development continues, analysis requirements become more specific and shift outside of the scope of CRO’s.

The selection of CRO’s is part of the development project and has a number of different effects. CRO’s are selected on past experience, the type of tests they can run, quality, cost, time allotment and more factors that need to fit within the development\textsuperscript{15}. The running of a study is always monitored be a representative of the research company. This necessary step ensures that the study is done the way it should and that there is a contact for any event that may occur.

CRO’s are not actively involved in the decision making regarding the strategic development of a compound. Their influence is limited to setting the specifications of the research studies done at their facilities. It is their role to supply objective information about a compound. It is in this area that the CRO’s might influence a project in a less than objective manner. According to one investigative research report [Radar, 2008], it is possible that a CRO has knowledge of the goals of the company and therefore can make the test results appear more optimistic. This was, according to that same report, motivated by the hope of getting new commissions after a job well done. As to the size of this problem and the risk involved, sources differ. While the investigation mentioned that this situation of influencing is a very likely situation, the actual verification of this during a project is impossible, as it would require an expensive rerun of the study elsewhere.

Each CRO has its own Standard Operating Procedures, output formats and information database which dictate the resulting data format and data. These are dependent not only on the facility and its researchers, but also on regulations set by the government of the country where the CRO is located. During the creation of a study, a request is made to research aspects of a compound, to which a CRO will respond with their study design. The study request and the design are then analyzed to come to an agreed study design which will be used. This changes the original study design, making the selection of the CRO an influencing factor in the study outcomes.

**Specialty service companies (SSC)**

Kinesis can fulfill the tasks that Evens describes as specialty services. These are companies that can supply services and expertise needed in a project. Specialty service companies are typically hired in cases where a company cannot execute a specific step in the development. Examples of services provided by such companies include statistical analysis, writing of medical reports\textsuperscript{16} and support in

\textsuperscript{15} As stated by project leaders and department representatives at Kinesis

\textsuperscript{16} Medical reports are highly specialized and detailed reports concerning findings done during a trial. The requirements for these reports are set by regulatory affairs, which not only affects the creation of the report, but also the content of it. This way, a regulatory requirement on a report can influence the design of a study indirectly.
regulatory reviews and affairs. Specialty service companies are not just a supplier of unsupported services; they can be an alternative for in house development as well.

Most of the original services described by Evens are on the operational level. A specialty service company is hired to perform a task, which is most often standardized but highly specialized. Like CRO’s, their goals will be only indirectly related to the goals of the project, making it unlikely for normal Specialty service companies to interact directly with a project’s running. An advantage here is that the output created by these companies is easier to check than that of CRO’s. The disadvantage is that, unlike with CRO’s, there is little monitoring possible during the execution of these tasks. Due to the high specialization and the lack of monitoring, the SSC’s task is a kind of black box in a project, a request goes in, (meta) data comes out, but there is little understanding how it is done by the research organization. This makes steering and checking these tasks highly difficult. As with CRO’s these companies are selected on many different factors, including past experience, reputation, cost and speed.

Indirectly these companies can have a large influence on project running. While not directly a part of the decision making, the influence of these companies has its origin in the direct influence these companies have on the creation of information. This is not only due to direct compound information determining the status of the compound, but also information quality has effect on project progress. These two factors will be explained in section 3.1: Information in Projects, on the measuring of the success of a project. Requirements for their work are usually set by more actors than just the hiring research organization. Regulatory offices set standards and requirements for official tasks, influencing their method of working. The SCC running the task requested by the RO will have to make sure that the requirements set by the research organization fit in their own methodology.

As mentioned, Kinesis is categorized in this group. They provide above mentioned services, and more. Among their service portfolio are project design, project running and management and study/trial management. These services are directly linked to development strategy and execution. This means that Kinesis can influence execution of any strategy. The fact that Kinesis is asked to develop the strategies and run the project will have a twofold influence on the project. First Kinesis uses its expertise to create the development strategy. Their view of a good strategy may differ from the one aimed at by the research company. The fact that Kinesis often has more expertise and experience than the research company may provide them with a lot of influence. Secondly, Kinesis running the projects may influence a project because they have the first and direct control. Both these influences give Kinesis a lot of power within a project, which is part of the use of the arrangement. They use this power for the benefit of the project, but while doing so, they encounter a tension between full communication with the sponsor and fast decision making [de Bruijn, 1999]. Even if Kinesis would provide full project management, including project design and expert analysis, they still see their role as consultants. This means identifying upcoming high level decisions and then supplying that and the information needed to reach a decision to the sponsor, who will make the decision himself. The sponsor’s confidence in and decision power given to Kinesis should be sufficient for Kinesis to run the operational part of a project correctly. Kinesis has the responsibility to use this power correctly and give insight in what they do so the sponsors stays confident in the relationship.
Kinesis makes the situation described by Evens [Evens, 2007] more complex. There should be a distinction between a “normal” project set up with an RO as developer and one in the Kinesis setting. In this, Kinesis is the coordinating force in a development, with the RO being their client. Any VC or management of the RO are then sponsors of the client. Considering network communications, an RO should have full information, while a VC should have their information provided based on the RO’s wishes. The research organization is theoretically the only actor with decision making power. All other actors (should) have an advisory role or present certain constraining factors, but it the research organization that runs the project and should have control over it.

**Communication and market research companies**

Within the scope of this thesis, communication and market research organizations play a small role, these organizations become more important as the development progresses. It is their function to introduce the new drug to the market and to make the medical world aware of the introduction. Although these companies are important for the success of a new drug, they have little to do with the scientific development of a compound.

The most relevant contribution of these companies is market research. Market research can help set requirements and standards, taking into account competitor products, ease of use and many other factors that are important for the consumer. This information is used to set the targeted clinical condition and later the indication for the compound. The information gained by these companies is important right from the start, even at the beginning of the development as objectives and criteria are derived from this information. As mentioned, in many cases, these organizations become more important once a product is closer to completion, i.e. when more actual and concrete information is available for these organizations to fulfill their role.

Large companies typically have their own promotional and marketing departments, though for most of the Kinesis’ sponsors, these departments are outsourced. The marketing of the product and the education of medical practitioners can only start once a product has a certain chance of success, which is usually only shown late in the project.

**Law and regulatory organizations**

The pharmaceutical industry is heavily regulated to protect the drug consumer against ineffective or potentially harmful medicines. During the development, each developer, whether it is a large company or a small one, will come in contact with regulatory control of different nations. Regulatory control has two important goals. The first goal is to ensure safety of drugs and drug development. This is not just the safety of a drug on the market, but also the safety of trial subjects during the development project. The second goal is drug improvement. Drugs that offer no significant change on already available drugs have the possibility of being refused market entry. A drug should have a distinctive quality that makes it better, or different from current products.
The market of these drugs is guarded by regulatory control organizations, such as the Food and Drug Administration (FDA) in the U.S. and the EMEA (European Medicines Agency) in Europe. These organizations guard the quality of the drugs, but also some of the legal aspects of the market, such as patent protection for special drugs and development requirements.

These organizations influence the development and the strategy by setting conditions and constraints from outside. This forces specific types of studies to be run, affect the order in which studies are run and the content of the studies to be safety compliant. The power of this actor is significant, as it is impossible to progress to certain phases of development without their go ahead.
Appendix B: Influences and effects on the drug development

Requirements and regulations

Rules and regulations in drug development are many and strict. Experience with safety effects have resulted in many regulations to protect the test subjects and product users. The requirements and regulations are not susceptible to change and are unique for each compound. Any rules and regulations originated from regulatory control have to be applied, even if this need becomes apparent during in the project. Some regulations are easy to implement, others require a thorough analysis of the regulations, compound and project before the effects of these regulations on a project can be understood.

Safety requirements

Safety requirements are among the more complex factors influencing drug development. These regulations dictate what potential adverse effects must be researched and to which conditions a medicine should adhere. This is a matter of ethics, ensuring that (test) users are not exposed to substances whose possible adverse effects are not known, or exposing them to an dangerous dose of the compound. The highly debated definitions of ethical make it difficult to set hard criteria for safety requirements. This is further complicated by the fact that the safety factors for which the criteria are set are not standardized. Each compound needs to be analyzed to define the unique safety aspects that need to be researched. The safety aspects and the criteria are translated into rules and constraints used for designing actions during the project. These rules and constraints, as well as the aspects and criteria used to create them will be checked by the regulatory organizations on completeness and ethics. It is the task of the RO to provide all relevant information to the regulatory organizations to perform this verification process, which requires highly detailed information. This becomes more complicated later on in the project when regulations dictate tests to be run in different countries, because each country has a different set of safety requirements, requiring customized trial designs.

Requirements on research sequence

Requirements are also encountered in the form of a compulsory research sequence, the order in which knowledge is gained. This can be expressed in two ways, the first is that actions May only start after specific other actions have been completed. The second way to express this is that a specific information or a minimum result is required. For example, rules may require a basic level of safety to be proven before the compound may be tested on humans. This requirement is one of the main structuring factors of the development template presented in section 2.3.

Regulations on research quality

Research in this industry has specific quality standards. There is a standard for performing good research, called Good Laboratory Practice (GLP) or Good Manufacturing Practice (GMP). A study
done by GLP or GMP standards is executed according to official rules and regulations that aim to guard the quality of the results. The GLP/GMP level is not a strict requirement when gathering information; studies can be done below GLP/GMP level and yield the same outcome. However, GLP and GMP are the only studies that are acknowledged as sources of information by regulatory offices [Evens, 2007], therefore important studies will always require at least one run at the GLP/GMP quality level. This is not the only reason for running studies to GLP and GMP standards. Results from GLP/GMP compliant studies are considered more complete and trustworthy, which offers companies an excellent way to gain confidence in the results of their compound.

**Documentation requirements**

Creating the documentation required by regulatory offices is highly specialized work. There are strict requirements to the document content, to ensure full compliance with the rules, SSC’s with specific knowledge are needed to create these documents. The documents contain all information the regulatory offices need to perform their checks, though it is possible to supply additional information to help convince the regulatory offices. This additional information is not part of the official format and should not be included in the standard document, but supplied separately. The FDA is currently working on a standardized format for of non-clinical data, (“Send”, meaning Standard for Exchange of Nonclinical Data [Papoain, 2004]).

**Communication with the regulatory organizations**

During drug development, there are at least two occasions where an official document has to be submitted to regulatory offices. The first communication is prior to human testing, for which a document called the Innovative New Drug (IND) report for the US and Clinical Trial Application (CTA) for Europe must be submitted. The document should list all the safety and therapeutic effect factors of the compound under development. The documentation is processed by the regulatory organizations during some months, though the RO does not have to wait this full period to start their studies. If there are no objections after the first month of reading the documentation, the trials may start. The other document must be presented when a drug is about to be released on the market. The New Drug Application (NDA) report for the US and Common Technical Document (CTD) for Europe contains all known information about the drug, as well as its proposed use, targeted population and even the design of the label on the container. This last step is the official step between trials and markets, and the Regulatory organizations do a full check on the new product.

Another occasion when regulatory control must be notified is when a serious adverse event occurs during human trials. At that time not only the controlling organization will want as much information on the event as possible, it will most likely also investigate the cause (for future reference) and the predictability of the event.

**Economic aspects**

In the economic aspects of drug research, two factors can be distinguished, the cost and the return of investment. As each study requires a financial investment to be made, the study bears information on the compound, which in return adds value to a project.
By far the largest part of the project budget is taken by studies and trials, followed by analysis and project management. Between the studies and analysis there are large variations in cost: some of the more elementary studies are relatively cheap costing only a few thousand Euros. Others such as large scale efficacy and safety tests cost several millions. Cost, like scientific and regulatory requirements leave some flexibility in planning. The cost of a study is usually determined per study type, many of the study’s details can be customized by the study designer. This gives a certain amount of control over the costs of the study and over the quality of the results. Options like selecting different CRO’s, setting the size of the study population or the duration of a study can change costs significantly. It is also possible to relocate studies to different times in the project. While this will not influence the cost of a study, it may be placed at a more financially stable point in the project.

Making a drug usable for children requires special pediatric research. Unless a drug is intended specifically for children, this research is not required for a drug to be allowed on the market. In many cases, this is postponed after the drug is marketed, if done at all.

The yield between studies can also vary greatly. Scientifically speaking, all information adds value to a project. As some studies are required by regulations, even finding nothing new adds value to a project, as it will allow the project to progress to the next step. The cost and the yield of a study are not always directly related, as a low cost test, such as the Ames test\(^\text{17}\), may give critical information.

There is difference between adding information and adding value to a project. Positive information on a compound’s performance adds value to a compound: if it performs better, it will sell better once it reaches the market. With more information, the project is further along its path, increasing the value of the project. There is also the possibility of negative information. Negative information adds value to a project, even when it means removing all value from a compound. Negative information is still useful for the project, it allows a change in development plan or in the worst case, enable the project team to limit the losses. Generally speaking, when a compound is further in its development, the economic value added by (positive) information increases.

In many projects, financial optimization and risk minimization are objectives that influence the project plan. This influence is not limited to the planning in time and location of studies, but affects them at a lower level, the design level. Taking the above factors into account, many RO’s try to do the most cost effective studies first, i.e. the studies with the highest yield and providing the most critical information per investment. Finding and plotting this project plan requires the combination of scientific output, project needs and financial expertise. Though the economic objectives are one of the foundations of project design, rules and scientific requirements will prohibit optimization on a purely financial basis.

\(^{17}\) A simple test to see if a compound is not mutagenic, which means dangerous to DNA or cause cancer. If a compound is mutagenic, its research is usually immediately stopped.
**Scientific aspects**

Within pharmaceutical development projects, one of the strongest influences on development progress is found in scientific compound results. The information on the compound dictates which and how aspects of the compound have to be researched. Discovering new information has the power to completely change a development project by changing the information needs. The process of updating the information and checking the effects is a continuous task during the running of a project. This process affects the whole structure of a project, the scientific results and decisions create a setting for the next decision or design. Ergo a decision made early in the project will affect the information supply and decisions later in the project.

An example of a factor of major importance for safety occurs in the area of cardiac effects. This covers analysis of the effects on heart functions and blood flow within a subject. Information on cardiac effects is gained by performing tests designed specifically for this purpose, but these tests do not present the whole picture. From other tests vascular, muscle and artery system, information is needed to give a (more) complete picture of blood flow safety. Only with the combined information of these studies it will be known if additional studies will be needed and if specific safety monitoring should be applied for current studies.

Scientific factors also influence the project by setting the requirements for actions and the order in which they are performed. The data that is the outcome of studies is complex, it requires analysis before results can be found. This means that following a study, an analysis must be planned. Occasionally, multiple studies are the source of one analysis. This requires the actions to be performed in a specific order and grouping.

If funds were not limited, it would be possible to create a complete research path, mapping all the effects of a compound on the human body. This is not the case however. Not only are funds limited, most of the knowledge from “complete” research will never add value to a project. Gaining full information on a compound isn’t always necessary; it isn’t even always the right way to go. The effects and working of compounds is so unpredictable that focusing on the primary parameters first is a safer way of planning the project. Once these are found to be acceptable, the risk of doing additional research is considerably less. No project is the same, each time the project team needs to analyze what information is needed from a scientific and compound development point of view. With current projects, most scientific dependencies have been implemented in the project template.

As preference and project strategies are set or changed, the perceived dependencies will change as well. Either the dependency is not there anymore, or it was decided to ignore it. Sometimes, assumptions are made on the behavior of the compound, as financial or time aspects make it necessary to skip research for this moment. Due to the unpredictability of the effects of the compound, only further research will prove if the assumption was correct. Hence, the correctness of decisions can only be determined in hindsight.
Competition

Competition introduces two factors a developer should take into account; these are time to market and product quality. These factors have an effect on the strategy and development, as each presents dangers and opportunities.

Time to market

The importance of time to market comes from two factors, patents and ‘the winner takes all’ settings of the industry. In the pharmaceutical industry the first product on the market will be winner of the market. Compounds introduced thereafter have increased rules (regulatory affairs require a distinctive effect), more marketing - a newly discovered cure is easier to market than a competitor product - and a shared market. Speed of development is essential if there are competitors researching a compound targeted at the same market. The other aspect that is affected by time to market concerns competitive production. The patent protection in this industry is not so much about compound information protection, but market protection. A conservative estimate is that once a patent is expired, three quarters of the market share will be taken over by generic drug companies within the first year. These companies are only required to show that their version of the drug is bio-equivalent, meaning that they have to show that it has the same effect. This vastly reduces their research and costs so they can supply much cheaper. The loss of sales after patent expiration makes speed an important factor in research even if there is no competitor developing a compound for the same market, as return on investments should occur before the patent expires.

If a product is not the first on the market, the product quality becomes important. In many cases, comparable products will not stand a good chance on the market. Only if a product has discernable qualities, such as better efficacy, or similar effects with fewer adverse effects, will it have a possible future.

Security

Information on a compound is guarded. Not only can presenting information endanger the patenting process, it will enable competition to better control their compound development, endangering the potential success of one’s own compound. Sharing information is done as little as possible in this network to ensure this security.

Opportunities

Competition also brings opportunities. There is the option of selling a product to a competitor or being bought by competitors, which may be considered a success from a business perspective. The future of the compound development is then in new hands and not always certain.
Appendix C: The phases of drug development

The development of a drug is divided into seven phases to manage different aspects of the drug, such as safety or dose setting. Each phase has specific objectives, which need to be reached to go to the next phase. These objectives set their own information needs. As phases progress, research is focused on different aspects of the drug, starting with safety requirements and progressing to effects and use requirements.

The most complete development template will have seven phases, starting at the Discovery Phase, going on to Pre-clinical Phase, Clinical Phase 1, Clinical Phase 2a, Clinical Phase 2b, Clinical Phase 3 and finally, Clinical Phase 4. Though the order of phases is the same in every project, not all phases are present in every project. Safety and other concerns sometimes require phases to be skipped or merged.

In research against cancer, the potential cure can be carcinogenic itself (it has the potential to cause cancer). While this is an unfavorable outcome, the beneficial effect can be strong enough to accept this safety effect. However, due to this safety issue, it is considered unethical to expose healthy volunteers to such substances and in such cases clinical phase 1 is skipped.

The figure below shows the phases in sequential order. The phases are successive and a project can never be in more than one phase at the same time. The project phases, in essence, determine what kind of research is allowed to be done: pre-clinical studies (studies not done in humans) are done in clinical phases 1 till 4 as well.

The discovery phase

The Discovery phase is the phase in which a compound or compound family is found. Officially, this is not a development phase, as this phase is focused on the identification of molecules that might be worth developing. However, results from this phase present information on the compound which is used as a basis to define the information need for the rest of the development, which is why this phase is presented. This phase results in compounds in which an initial mechanism of action - the way a drug interacts with the body - is found that is expected to be beneficial against certain clinical conditions. Also, results from these tests are not always as complete or certain as needed, so it is required to verify the data from this phase on completeness. Perhaps contrary to intuition, most compounds are not discovered with a specific disease or effect in mind. Later in the project, the mechanism of action will be linked to a clinical condition; this happens sometimes as late as clinical phase 2.
The non clinical phase

The actual development of the compound begins with the non clinical phase. This is a phase of mostly in vitro and in vivo studies on animals. There are three main goals of this phase: First, to select a “best” compound to develop from a compound group. This goal is not always present and is only needed if multiple compounds were presented after the discovery phase. Another important goal for this phase is to study the non clinical safety of the drug to see if testing on humans (which is clinical testing) is possible. The third goal is to find a working formulation, a way the drug is administered to a user.

Lead Compound selection

In case multiple compounds look promising a candidate drug is selected to continue the project with. Selection is done by comparing the known effects of all the compounds. When lead compounds perform very similarly, this selection is difficult and it can be decided to continue with multiple lead compounds until more information is found. There is a risk in this, because each compound, no matter how similar it is to others or to previously researched compounds, requires its own studies, budget and time. The next phase, clinical phase 1, always starts with a single compound. This is illustrated in the figure on the right.

Figure C 1: The continuous process or selecting a lead compound

Non clinical safety

The non clinical safety testing is finding out which tests are required to allow use in humans. It is one of the earliest steps where in-depth knowledge of a specific area of the pharmaceutical field is needed. Analysis of the compound, its type, known issues in chemically similar compounds and known effects all influence what tests need to be done and what specific data will be needed from these tests. In simple compounds (such as small molecule type compounds), this testing is fairly standardized in around five or six tests, as can be seen in Appendix A: Development Template. Today’s compounds are often more complicated and lack this standardization. These will require a complete analysis of all effects that might be encountered. The effects on a project are that selection and design of studies is much larger and covers a wider range of variables than “classic” compounds. Because there is no standardization, it is impossible to state when non clinical safety studies will cover the safety research sufficiently. The selection and design of studies need to be based on the analysis of (expected) chemistry and biological mechanisms, not on known output parameters.
Formulation

A formulation has to be made to be able to test a substance in vivo and in humans. A formulation is a way a drug substance is administered (provided) to a user. There are 106 different types of administration, each with their own attributes. The preferred administration is oral (taken in through the mouth), followed by dermal, nasal and intravenous, all of which have subtypes. A formulation is made up of two parts, the active ingredient and the excipients. The active ingredient is the drug itself, the excipients are all the extra substances added to the drug to ensure stability, availability and ease of use from the time the drug is created, packaged and used. Research in this field is done by the department Chemistry, Manufacture and Control (CMC) in order to find an optimal formulation. A formulation needs testing and often refining. This last step is often a reason of redoing some studies. Adding new excipients to a drug may require new tests or redoing tests. Even a new production process of any of the components may be a reason for new testing.

Generally there are two approaches for the creation of a formulation in the non clinical phase. The first is to immediately create a formulation that can be applied to humans, so all tests will be valid the first time. A second strategy is to create a simple formulation specifically for this phase. This is usually faster and cheaper than the first strategy, but there are some dangers. The difference in formulation can affect the outcomes of the studies, giving different results than would be actually encountered then when using the “human” formulation. Also, a human formulation will still have to be made and this now must be tested on bio-equivalence, i.e. are the results similar enough to accept the studies done with the first formulation.

Non clinical safety testing can only end once the safety information has been submitted to and approved by regulatory offices\(^{18}\). In this phase, human testing is not allowed yet, so only relatively short and cheap in vitro and in vivo studies are used.

Clinical phase 1

Once the preliminary safety of the compound for humans has been established and a usable formulation is found, the first human trials can start. This is called Clinical Phase 1 and is focused on safety. In this phase a small group of healthy volunteers are asked to take the compound in order to find possible adverse effects and the extent of the effects of the compound. Generally no efficacy information is sought after in these studies, as the main goal is to find the actual safety effects in humans. During this phase, non clinical studies are still run to help discover possible safety issues. Results from these studies can help narrow down the clinical condition the drug will counter.

A second goal is to check the formulation. This is a first test to see if the chosen formulation will actually do what it is supposed to do for human users. If no adverse effects are observed, one may have found an ideal drug. Another possibility is that a formulation is not working at all and the drug is not delivered where it should be.

\(^{18}\) This is the submitting of the IND, as was explained in section Appendix B.
Whereas the non clinical phase is very flexible in its design dependent on the drug type, the first clinical phase is a lot more standardized. In many projects there are a fixed number of tests and trials that give the information needed in this phase. The actual make up of the tests, i.e. what and how things are measured will vary, but the general structure is fairly similar to a CRO’s projects.

**Clinical phase 2a**

If the safety effects found in Phase 1 are considered to be acceptable, the trials can move to patients in phase 2a. This is the first phase in which the product will be tested on patients with a certain clinical condition.

Phase 2a is meant as a first efficacy test. To find out how well a drug works and the clinical condition it will counter will be decided.

During trials, the patients with this clinical condition will be given the drug and the effects of the drug on the patient and the clinical condition will be analyzed.

![Diagram](image)

**Figure C 2: The steps in narrowing down the clinical condition and indication**

This phase also has the goal of finding a dose range. The dose range is the range defined by the minimum exposure to the drug that provides a measurable beneficial effect and the maximum exposure beyond which the adverse effects become intolerable. The dose range found by these studies is called the window of opportunity. It is possible that during this phase the formulation requires a change. This may be because the bio-availability\(^\text{19}\) of the compound is not right: the drug is released too fast, too slow, at the wrong place in the body, etc. Many of these effects can only be seen in a larger scale test on actual patients.

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\(^{19}\) The bio-availability of a drug states if and where the drug was present in the body after using it. There are many obstacles for a formulation to deliver the drug at the correct location in the body and the delivery system (the administration and the excipients) needs to be created to overcome these obstacles.
Phase 2a is also the phase where the clinical condition is determined. A clinical condition can be described as the ailment a person is afflicted with. This can be as vague as having a headache to specific as having a certain disease. In case the target can be defined specifically, this is called an indication. The indication is a very specific designation of the clinical condition, taking into account the clinical condition, possible subtypes of the condition, the progress of the condition, the previous treatments the patient has experienced, the mechanism of action of the drug and the condition and the known adverse effects.

The targeting of the indication can differ between very broad scoped processes to a very fine targeting of a sub-group of a condition. For example: a drug has been found to relieve pain. Only in Phase 2 was it selected to develop this into a relief against headaches. Another example of targeting in a more narrow way: a drug was developed against HIV. Later the indication was specified for HIV patients that had experienced treatment before (this makes the virus more resistant) and were carrying a specific viral strain that had developed resistances to certain other drugs.

Interaction effects with food and other drugs are researched in this phase as well. This can be both a beneficial or adverse interaction, which often leads to instructions how to use the drug, such as having it before dinner, or that a drug should not be used in combination with alcoholic drinks.

**Clinical phase 2b**

The main goal of this phase is to set the drug dose. Setting the dose of a drug is a tradeoff between beneficial and adverse effects. A dose is set by trying out different dosage, based on the dose range found in clinical phase 2a. A dose is set that maximizes the beneficial effect while having acceptable adverse effects compared to the beneficial effect.

**Clinical phase 3**

In Phase 3, the dosage found in phase 2b will be used on a larger scale test to find the full effects of the drug in that dose. Again the effects of the drug are compared to see if the current dosage is acceptable.
If the results here are good, then the RO can submit the found results to regulatory offices (in form of the NDA as explained in appendix B). The regulatory offices will analyze the findings and check them\textsuperscript{20} before allowing a drug on the market. This is the final step before the marketing of the drug.

**Clinical phase 4**

After marketing, results will be closely monitored and subsequent research is done if required. This is considered phase 4. Once a drug is on the market, the exposure to the population will be large enough to find any effects that were undetectable in the large scale tests done during development.

\textsuperscript{20} Checks are made on the safety aspects, which includes everything up to the packaging and description on the package. Also a check is made if the drug has distinctive qualities, which means that it is significantly different from existing drugs. This does not automatically mean a drug has to have a better effect, it can also be expressed in having to take it fewer times a day (better ease of use) or having less adverse effects.
Appendix D: Project team and hierarchy

The total development of a compound requires the contribution of hundreds if not thousands of people. Most of these are researchers, analysts and medical writers. Of all these people, only a small group will be involved in controlling the project. For controlling, there are sixteen different roles, each of these roles is responsible in a specific aspect of the development. Not all of these roles are as unique or as influential as others. The higher one gets in the project team hierarchy, the less instances of one role will be found. At the top, there is the project management, representatives of all the departments and a project leader, that steer the project, this is the project team.

With these specific roles filled, a development team has the scientific expertise to fully develop a compound. As was mentioned in the analysis of the development of a compound, there is more to drug development than purely the scientific aspect. Regulatory affairs and marketing can have an influence on the development, which can result in these departments having a representative in the project team as well.

A role is different from a person. A role is a function, a set of tasks, the person can fulfill. For example, an expert on clinical trials can have the role of clinical department representative, but not the role of CMC expert. Multiple roles can be assigned to a person, as is often done in Kinesis.

In the table below, the core project team roles are presented:

<table>
<thead>
<tr>
<th>Role</th>
<th>Category</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project leader</td>
<td>Leadership</td>
<td>Organizes and manages the project</td>
</tr>
<tr>
<td>Sponsor’s representative</td>
<td>Leadership</td>
<td>Decision maker (or Decision maker’s representative)</td>
</tr>
<tr>
<td>Non Clinical department representative</td>
<td>Expertise</td>
<td>Steering the project, design and managing of all non Clinical studies</td>
</tr>
<tr>
<td>Clinical representative department</td>
<td>Expertise</td>
<td>Steering the project, design and managing of all Clinical studies</td>
</tr>
<tr>
<td>CMC representative department</td>
<td>Expertise</td>
<td>Steering the project, design and managing of production, formulation and container fabrication</td>
</tr>
</tbody>
</table>

Table D 1: Project members and their tasks
The project team

The project team is the group of people that run the project. To do this, a project team identifies three main roles, roles that are in the top of the project running. These roles are that of the project leader, the department representatives and the sponsors’ or management representative. The core of any development team consists of at least five specific roles, as there are a minimum of three departments, non clinical, clinical and CMC needed for their expertise.

Project leadership

The highest ranks are those of the project leadership. This consists of two roles, the first is the “official” project leader. Compliant to project management theory, he or she manages the project, indentifies issues and gets the team on solving them. The second key position is that of the sponsors’ or management representative. This is the actual decision maker on major (strategic and some tactical) decisions. If a compound would be developed in house, this would be a higher manager or board that has decision power within the company.

Project leader

The project leader is the head of the project team. Project management theory identifies a major role for the Project Leader, he is the person that combines all different expertise and tracks strategy and planning. In the Kinesis case, this role is used quite similarly. The project leader creates the project team, facilitate the design of the project and to keep it on track during the run. Together with the sponsor or management representative they will select the strategy and will be responsible for keeping it. During the run, he will often facilitate the sharing and combining of expertise, as well as provide the communication of the project status to the sponsor.

In Kinesis setup, the project leader is often chosen from one of the department representatives, as all project leaders have started in one of the departments and have grown in experience within the company. To decrease size and keep the project team as small as possible, the project leader often has a double task, being the project leader and the department representative at the same time.

The project leader has decision power on many of the tactical decisions. Once a strategy is set, this has to be filled in with the project plan. It is the task of the project leader to get this plan created. To do this, actions have to be planned. The actual selection of studies is done based on the information of the whole project team. Planning the actions is dependent on the different dependencies that are present in a development project and is the responsibility of the project leader.
The sponsor’s representative

This project member is the contact of the client, sponsor or higher level management that is ultimately responsible for the project. He is a delegate with the high level decision making power, in effect making or relaying all the strategic and sometimes tactical decisions. Different project can have different names for this project member, depending who he reports to, a client company, higher management or a VC. When the term sponsor’s representative is used, it is meant as the project member that has the delegated power to make decisions.

Occasionally there will be multiple sponsors, such as when a client company is backed by a VC. It in those cases, it is possible that there are multiple sponsor representatives, if each representative has decision power. In such cases, the information presented to the sponsor’s representatives should be identical.

This representative has the power to set the objectives and strategy, as well as make many of the tactical decisions and strategic designs. For most of these decisions, the project team will have to provide information however, such as what realistic objectives for a compound are. The role of sponsor representative does not require knowledge of drug development, a good project team will have all required expertise from other roles.

Usually having neither expertise nor project management skills, the sponsor’s representative is very dependent on the expertise and information received from the project leader and team. Especially if this team member does not understand the wisdom of a decision, it should be possible for him to retrace the steps and logic for decisions made, no matter at what level. As this representative represents the sponsor of the company, it should be of utmost importance for a project to have this participant up to date and informed. Lacking this would break one of the nine rules of project management, communication with the powers that be.

Project experts

The project experts are the different departments that are required to develop a compound. The knowledge of these departments is very different, based on specific biology and chemistry disciplines within the pharmacology.

Non clinical

The main focus of the non clinical department lies at the start of a project. It is their main task to find the effects on safety a compound may have. The role of the non clinical department does not end after the non clinical phase is finished. During later phases, sometimes even as late as phase three, non clinical trials continue to be run. In later parts of the project, the non clinical department has less of an exploratory character, but more that of guarding the safety limits that have been researched or not.
**Clinical**

The clinical department is specialized at running trials with human test subjects. The clinical department will be able to present information on the behavior of the compound in humans, which is needed to set the dosages and refine the formulation. Not active in research before the first clinical phase, this department should be attending the non clinical phase to help set study parameters to enable human testing.

**Chemistry, Manufacture and Control (CMC)**

The experts in Chemistry, Manufacture and Control are the creators of the drug. This department researches the production of the compound and the product. This is a task that, dependent on the strategy, might be separated from the phases. One of the non clinical phase goals is to develop a working formulation for humans, is their department. The compound information concerning the production time and production costs are important information for this department, compounds too expensive or difficult to make cannot be tested successfully.
Appendix E: Decisions

In this appendix, the identified decisions are analyzed on the control type, the level of detail, who the decision maker is and what kind of decision output type is presented.

Project creation

<table>
<thead>
<tr>
<th>Decision:</th>
<th>Control type</th>
<th>Level of detail</th>
<th>Decision maker</th>
<th>Type of decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identify objectives</td>
<td>Managing / Steering</td>
<td>Strategic</td>
<td>Leadership</td>
<td>Open</td>
</tr>
<tr>
<td>Identify fields of expertise</td>
<td>Steering</td>
<td>Operational</td>
<td>Project Leader</td>
<td>Closed</td>
</tr>
<tr>
<td>Select project members</td>
<td>Managing</td>
<td>Operational</td>
<td>Project Leader</td>
<td>Closed</td>
</tr>
<tr>
<td>Select and set the objectives</td>
<td>Managing / Steering</td>
<td>Strategic</td>
<td>Project Team</td>
<td>Open</td>
</tr>
</tbody>
</table>

Information need determining

<table>
<thead>
<tr>
<th>Decision:</th>
<th>Control type</th>
<th>Level of detail</th>
<th>Decision maker</th>
<th>Type of decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determine characteristics</td>
<td>Steering</td>
<td>Strategic</td>
<td>Project Team</td>
<td>Open</td>
</tr>
<tr>
<td>Determine constraints</td>
<td>Steering</td>
<td>Tactical</td>
<td>Project Team</td>
<td>Open</td>
</tr>
<tr>
<td>Create research questions</td>
<td>Steering</td>
<td>Strategic</td>
<td>Project Team</td>
<td>Open</td>
</tr>
</tbody>
</table>
### Planning actions

<table>
<thead>
<tr>
<th>Decision</th>
<th>Control type</th>
<th>Level of detail</th>
<th>Decision maker</th>
<th>Type of decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inventory needed actions</td>
<td>Steering</td>
<td>Operational</td>
<td>Project experts</td>
<td>Closed</td>
</tr>
<tr>
<td>Determine planning constraints</td>
<td>Managing / Steering</td>
<td>Operational</td>
<td>Project Team</td>
<td>Open</td>
</tr>
<tr>
<td>Decide what actions to use</td>
<td>Managing / Steering</td>
<td>Strategic</td>
<td>Project Team</td>
<td>Closed</td>
</tr>
<tr>
<td>Design action</td>
<td>Steering</td>
<td>Operational</td>
<td>Project experts</td>
<td>Open</td>
</tr>
<tr>
<td>Determine critical path</td>
<td>Managing</td>
<td>Tactical</td>
<td>Project Team</td>
<td>Closed</td>
</tr>
<tr>
<td>Plan actions</td>
<td>Managing</td>
<td>Tactical</td>
<td>Project Team</td>
<td>Closed</td>
</tr>
</tbody>
</table>

### Compound decisions:

<table>
<thead>
<tr>
<th>Decision</th>
<th>Control type</th>
<th>Level of detail</th>
<th>Decision maker</th>
<th>Type of decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Select lead compound</td>
<td>Steering</td>
<td>Strategic</td>
<td>Leadership</td>
<td>Closed</td>
</tr>
<tr>
<td>Select formulation</td>
<td>Steering</td>
<td>Strategic</td>
<td>Leadership</td>
<td>Open</td>
</tr>
<tr>
<td>Set dose range</td>
<td>Steering</td>
<td>Strategic</td>
<td>Leadership</td>
<td>Semi Closed</td>
</tr>
<tr>
<td>Set dose</td>
<td>Steering</td>
<td>Strategic</td>
<td>Leadership</td>
<td>Semi Closed</td>
</tr>
<tr>
<td>Set clinical condition</td>
<td>Steering</td>
<td>Strategic</td>
<td>Leadership</td>
<td>Semi Closed</td>
</tr>
<tr>
<td>Set indication</td>
<td>Steering</td>
<td>Strategic</td>
<td>Leadership</td>
<td>Closed</td>
</tr>
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</table>
### Project guidance

<table>
<thead>
<tr>
<th>Decision:</th>
<th>Control type</th>
<th>Level of detail</th>
<th>Decision maker</th>
<th>Type of decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>To start or stop an action</td>
<td>Managing</td>
<td>Operational</td>
<td>Project Leader</td>
<td>Closed</td>
</tr>
<tr>
<td>Select the next step in the project</td>
<td>Managing / Steering</td>
<td>Tactical / Strategic</td>
<td>Project Team</td>
<td>Closed (one open decision)</td>
</tr>
<tr>
<td>To go to the next phase</td>
<td>Steering</td>
<td>Strategic</td>
<td>Leadership</td>
<td>Closed</td>
</tr>
<tr>
<td>To re-evaluate the project and redesign it</td>
<td>Managing / Steering</td>
<td>Strategic</td>
<td>Project Team</td>
<td>Open</td>
</tr>
<tr>
<td>To change the project strategy</td>
<td>Managing / Steering</td>
<td>Strategic</td>
<td>Project Team</td>
<td>Open</td>
</tr>
</tbody>
</table>