Challenges in Shortening New Product Introduction in the Pharmaceutical Industry

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Challenges in Shortening New Product Introduction in the Pharmaceutical Industry

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Abstract
Drug developing companies are forced to utilize the effective protection of the patent by focusing on shortening the new product introduction [NPI] process measured as Time-to-Market [TTM]. Here the NPI process is considered and the trade-offs, which have to be address in the future are identified. This is done through a case study, which identifies the tasks involved in the NPI process and analyzes their interdependence. The scientific literature is reviewed and a series of observations from the case study are made. This results in an identification of the major focus areas for reducing TTM.

Keywords: New Product Introduction; Time-to-Market; Case Study

Introduction
The pharmaceutical industry develops and produces drugs for alleviating illnesses. The most significant activities in the industry consist of drug development, production of the Active Pharmaceutical Ingredient [API] called primary production and production of the drug dispensing system, e.g. vials or pills called secondary production. Companies in the industry can perform any number of these activities in different organisational constellations. Lately, increasingly more elaborate collaborations and partnerships have emerged. Generally speaking the industry can be divided into two groups of companies; drug developing companies and manufacturers of generic off-patent drugs. In this paper attention is given to the drug developing companies and the production of the API. Secondary production is given less attention, since it resembles traditional part production and the methodology from this area applies.

Developing and launching a new drug cost a significant amount time and money, since new drugs have to go through series of clinical trials prescribed by regulatory authorities. These trials consist of testing the drug on cohorts of patients and monitoring their reaction to the drug, while other patients are given a placebo and are used as a reference group. The trials should prove not only the efficacy of the drug, but also find possible side effects and the pharmacokinetic properties of the drug etc. Each country has its own authority, which need to approve the drug. Best known is the Food and Drug Administration [FDA] in the US. In Europe there are three ways of getting an approval. Either the authorisation is coordinated by the European Medicines Agency [EMEA], which forces approvals in one member country to apply in another. Else the company can try to get the drug approved in one country and thereafter get others to

mutual recognise that approval or the company can just get it approved in each individual country. Common for all authorities in all countries is that they need to approve the drug before it can be sold in the respective countries. Depending on the results of the clinical trials they may approve the drug, reject it or require more trials or other changes thereby delaying the launch of the product.

The development of a new drug requires significant capital investments, has a high risk of failure and takes many years to complete. According to (DiMasi, 2002), the average cost is 802 million US$ for developing a new drug, which has a 21.9 % chance of getting through the process and takes 11.9 years to develop. Hence, it is most often large pharmaceutical companies or groups of smaller companies who enter this process. The risk is worth running, since the patent protection of the drug offers a time-limited market monopoly. Patents last for 20 years and are normally filed after the discovery of the drug. As 11.9 years are spent on developing it, only 8 years of effective market monopoly are left. When the patent expires cheaper generic substitutes are readily available and sales suffer as a consequence. Getting the new drug into the market sooner thereby making better use of the patent protection is the best way for the developing companies to increase the total lifecycle revenue of a drug. Therefore pharmaceutical companies are focusing their efforts on reducing the Time-to-Market [TTM] of their new drugs.

In the next section the research questions are outlined followed by a description of the research methodology. A case study carried out in a drug developing company is described which was used to analyse the activities involved in the new product introduction process. This resulted in a project network, which shows the structure of the process. Afterwards the literature and its relation to new product introduction process are described and finally a series of observations from the industry are stated.

Research Question and Methodology

First an overview of the new product introduction process is needed, which is the reason for the first research question.

Research Question 1 [RQ1]:

What major tasks are involved in the new product introduction process in the pharmaceutical industry and how are they interrelated?

The aim is to define a generic set of tasks including precedence relationships for identification of the critical activities. This identification is done on the basis of a case study plus interviews from several other companies. The next step is to consider what previous work has already been reported in the scientific literature.

Research Question 2 [RQ2]:

How does the scientific literature relate to the new product introduction process in the pharmaceutical industry?

The central question, which remains to be answered relates to how the TTM can be improved and which processes to focus on. During the interviews with managers a series of observations were made, which may clarify this.

Research Question 3 [RQ3]:

Which tasks have to be addressed to reduce Time-to-Market for the entire new product introduction process?

Sample Selection

The main data input for this article comes from a series of interviews done with managers from the industry. Due to the large size of pharmaceutical companies and number of people involved in the new product introduction process, managers from a variety of functions such as R&D, Production, Supply Chain functions, Regulatory Affairs and Marketing have been interviewed to obtain a complete picture of the process. Only from one company, the case study company, have all managers in these positions been interviewed. This case company forms the centre, but as stated in (Eisenhardt, 1989), more cases are needed to prove generality and validity. This has been achieved through control interviews for all management functions at 6 other companies.

The involved companies are all located in the greater Copenhagen and Malmo area in Zealand, Denmark and South Sweden. This area is known as Medicon Valley for its high density of pharmaceutical and biotech companies. These companies were chosen in part due to their geographical location close to the university and in part for their willingness to participate in the interviews.

Interview Protocol

As the nature of this project is exploratory, the form of a semi-structured interview was chosen. In this interview form, a structured list of questions is prepared in advance. But during the interview the interviewer can skip some questions and go in depth with others, depending on how the interview evolves. This is suitable as it helps keeping track of the interview, while allowing the interviewer to explore interesting new statements offered by the interviewee. Since most managers' working knowledge of the involved planning and execution of tasks in the new product introduction process was normally confined to a few tasks within their own responsibility area, it made no sense to spend much time on probing for answers outside their respective area of interest.

After a short discussion of the managers' responsibility area, he/she was asked to identify important tasks in the new product introduction process and point to major bottlenecks and problems in the process. This was done on the basis of a project network structure, which was iteratively developed throughout the interviews. With this information it was also possible to find the tasks that prolong the market introduction and lead to an unnecessarily high TTM.

Afterwards questions to all tasks in the process were posed and the manager answered as best he/she could. This served to establish knowledge of the tasks the manager worked with or was responsible for and observations of weak practices were made.

Data Collection

All the interviews were conducted from December 2009 to March 2010 and in all 14 managers from 7 companies have been interviewed. All interviews were digitally recorded for later use and sketches of how to improve the project network were gathered from the interviews. Validity and reliability was ensured by having control interviews for each manager position type as mentioned in 'Sample Selection'.

Case Study

The case study builds on interviews and information gathered from a pharmaceutical company, which for confidentiality reasons shall remain nameless. The company is a drug developing pharmaceutical company, which develops and manufactures a range of APIs and final drugs. All drugs are of similar chemical structure and are produced at several multi-purpose batch plants in Europe. The R&D organisation including a pilot plants use up more than 20 % of the annual revenue. In all 8 managers from across the

organisation were interviewed such that the complete new product introduction process in the company was covered.

The new product introduction process is organised in a classic matrix structure, which, as became apparent from interviewing the other reference companies, is commonly used in the industry. After the development of a series of new compounds, the most promising are chosen to be further developed and get assigned to a development team. The development team consists of specialists from the different functions in the company i.e. production, R&D, marketing and regulatory affairs. The team's composition depends on the stage in the new product introduction process of the drug. Marketing is involved in the beginning and end of the process to evaluate economic feasibility and prepare forecasts. Production and Supply Chain managers are increasingly involved, the further along the project proceeds, starting during capacity planning and the design of the production process. Under the responsibility of the R&D department, the production of prototype API for the clinical trials is done in the pilot plants, which are not intended for large scale production. Both R&D and Regulatory Affairs are involved all the way from conception of the drug to final approval. Decisions on whether to continue the development of the drug are taken on revision meetings with the top management.

Identifying the Project Network

During all interviews, a project network of the new product introduction process was presented and each interviewee was then asked to suggest changes in how they perceived the project network structure. Through this iterative process the project network seen in Figure 1 was created. The project network involves three key functions in the company (R&D, Production and Marketing) and those activities carried out by the Regulatory Authorities. The length of the tasks in Figure 1 is not indicative of the task lengths or the resource consumption, but helps indicating the timeline in the process from patent filing to patent expiration.

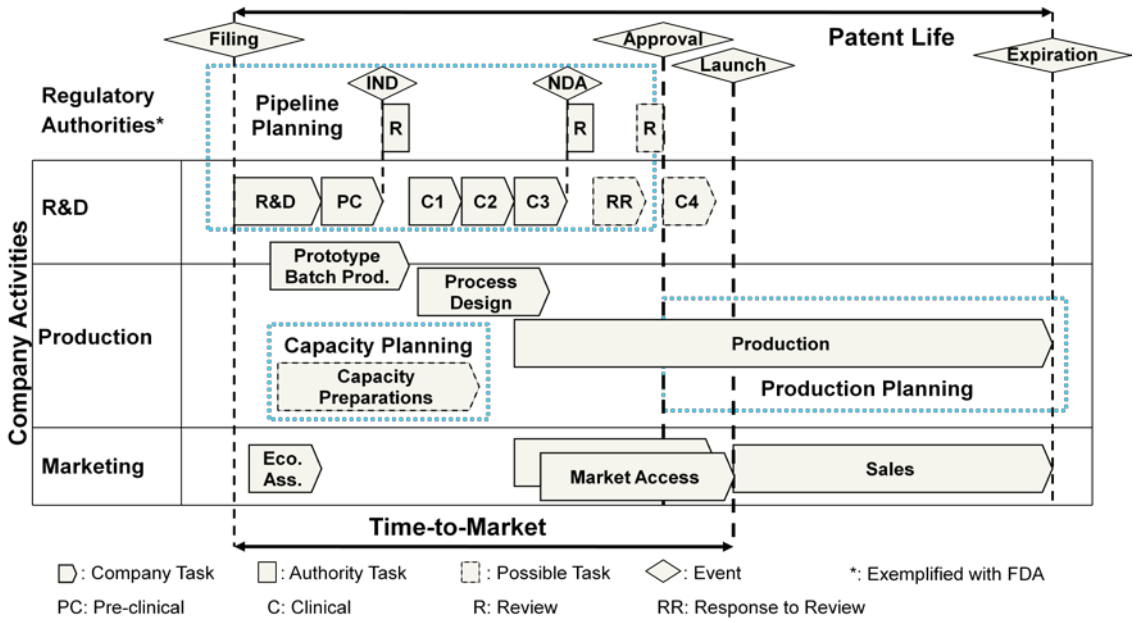

Figure 1 - Project network representation of the new product introduction process. NB: Task length does not represent task duration.

The tasks of the Regulatory Authorities are found at top of the network. R&D and Regulatory Affairs make up the R&D category. Here the first main task is the conception of the drug itself (cf. the R&D task). It is at this time the application for the patent is filed and the patent life starts (cf. the filing and expiration events). Next, initial studies of the drug are made in the pre-clinical trials (cf. the PC task). Based on the animal experiments in the pre-clinical trial, the documentation is sent to the authorities, here illustrated for the FDA, for review (cf. the first R task) as an Investigational New Drug application [IND]. If it is approved, the company can start the clinical trials (cf. the C1-C3 tasks). After these have been completed, documentation is sent as a New Drug Application [NDA] (cf. the event NDA) for a final review (cf. the second R task). The drug can either be completely rejected, completely approved or the authority can request more data thereby delaying the approval. This will require the company to respond to any comments from the authority and possibly produce the requested data (cf. task RR) before final review and the approval can be given (cf. the task R and the event Approval). A final clinical trial may also be needed after the approval of the drug, if the authorities or company sees the need for one. This could for instance be to try the drug on smaller patient segments such as children or pregnant women. Though the authorities' requirements are difficult to live up to, they are generally clearly stated as guidelines. The uncertainty of approval arises from the company's interpretation of these guidelines. The uncertainty of the trials comes from the difficulty of predicting how patients respond to the drug. These uncertainties are a clear risk for all tasks carried out parallel to the clinical trial. If a trial fails, prepared capacity becomes idle and work on other tasks become worthless. In the worst case the entire drug is abandoned or rejected and the company has nothing to show for its investment.

The production of prototype batches in pilot plants for the clinical trials (cf. the Prototype Batch Prod. task) is in some companies a R&D task and a production task in others. Production and supply chain functions are then much stronger involved during the design of the production process (cf. the Process Design task) which is done simultaneously with the clinical trials. Depending on the production method and current capacities, additional production resources may have to be made available (cf. capacity preparation). This could either be by clearing capacity at existing production lines or by expanding production facilities with new equipment or even factories. The reason capacity preparations are done in advance of the process design is that it may take that a long time to find equipment or build a factory. For the case company all production processes are so similar, that the same equipment is used. Process design is often more process tweaking than fundamental redesign. This relation between capacity preparation and process design may be different for other companies. The production of the drug then starts before the approval is gained as three high quality and identical batches have to be produced for the authorities (cf. the Production task). Furthermore, API inventories are normally filled before the market introduction (cf. the launch event) in order to fill up the market immediately after approval or market access has been gained. The production continues until the drug is taken of the market.

In addition to forecasting and promoting the sales volume (cf. the Sales task), marketing is also involved in economical assessments of a drug's potential early in the process (cf. the Eco. Ass. task) and in preparing the entry into new markets (cf. the Market Access task). The latter task consist of further identifying the economical benefit of entering the country or market but also of planning and conducting negotiations with local authorities to secure subsidies. As new approvals and subsidies have to be negotiated for each authority, this process is repeated in each country or market for each drug; hence the cascade in Figure 1.

The remaining tasks involved in new product introduction are not shown here, since they consist of traditional tasks also found in other industries such as procurement and distribution. It is important to note, that TTM is measured from the patent filing to market launch of the drug. This is seen in the precedence relationship identified through the interviews in Figure 2. The precedence relationship is illustrated as a directed graph going from patent filing on the left side to market launch on the right side. The structure of the tasks from Figure 1 is kept. All inputs enter from the left side and outputs exit from the right.

All the interviewed managers pointed to the clinical trials as the major bottleneck in the process. In addition it was mentioned, that several managers' main responsibility was to keep their task off the critical path i.e. to not delay the process. After gaining the approval, it would either be the subsidy negotiations or production that would slow the product launch. As the project network in Figure 1 has been created and the precedence of the tasks set in Figure 2, RQ1 has been answered.

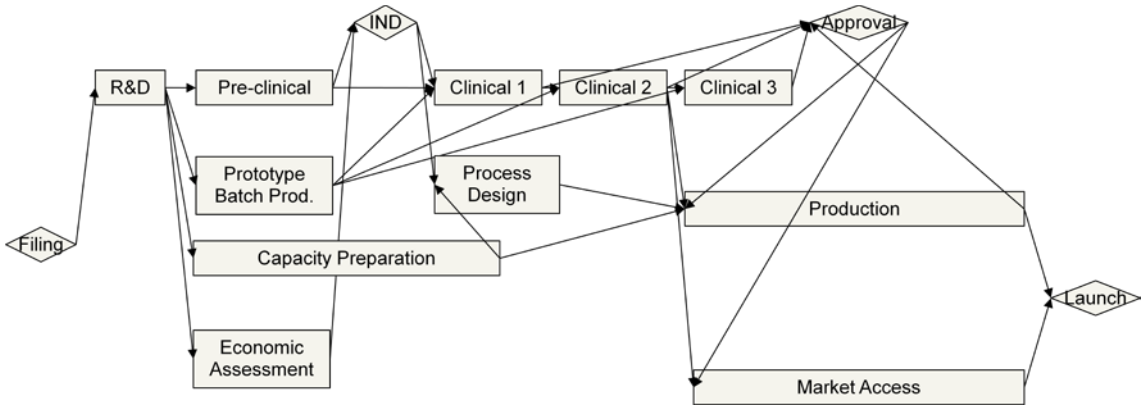

Figure 2: Overview of the identified precedence relationship illustrated as a directed graph.

Locating Literature in the Project Network

As can be seen in Figure 1 marked with three dotted boxes, previous contribution in the literature has addressed some of the activities in the new product introduction process. The boxes are here drawn around the main activities they are meant to plan. These areas are describes later in this section. The review only covers literature for operations planning.

When looking for literature on reducing the TTM, only a small fraction considers the pharmaceutical industry. No contributions have been found by the authors, which aim at reducing the TTM by effectively managing the operations involved in the new product introduction process.

A large amount of work has been found in computer aided process engineering. In (Papageorgiou, 2009), the author describes the latest advances in supply chain management for the entire process industry focusing on uncertainty and financial issues. More directly aimed at the pharmaceutical industry is (Shah, 2004). Here the current trends in the pharmaceutical industry are listed, which are all relevant for the new product introduction process. The trends include fewer potential research compounds, shorter effective patent protection, more generic substitutes and more price focused customers and authorities. The main contribution of (Shah, 2004) is a classification of the major areas found in the literature for the pharmaceutical industry. They are:

- Pipeline management or planning

- Capacity planning
- Simultaneously pipeline and capacity planning
- Production planning and scheduling
- Process development and plant design
- Supply chain simulation

There is given no relation to how these planning areas relate to the observed trends. Only first 4 planning areas are really interesting in the new product introduction context as can be seen in Figure 1.

Pipeline planning is the discipline of planning which products in the pipeline to develop further in the face of uncertainty involving the approval. One of the central contributions here is (Jain and Grossmann, 1999), where the authors were the first to also schedule the development tasks with limited resources.

In (Papageorgiou et al., 2001) the authors were the first to investigate the impact of production cost and available capacity on profitability. Their MILP model tried to capture all the business rules involved in capacity planning. But their model did not account for the uncertainty resulting from the clinical trials. This was later addressed in (Gatica et al., 2003), but here pipeline planning decisions were not included. That has only been done in (Maravelias and Grossmann, 2001), which is the only work to date that combines pipeline and capacity planning.

Production planning is arguably also related to the new product introduction process, since the above mentioned models include some production planning elements, but only on very aggregate level; usually annual quantities. More specific mentioning of production planning has not been found. Nor is the new product introduction mentioned in (Méndez et al., 2006) or (Shaik et al., 2006), the two most commonly cited review papers on production planning in this field.

It seems that there is a gap in the literature with regards to an approach for reducing the TTM. Though some literature treats the new product introduction process, none of the contributions addresses the industry's demand for a methodology aimed at reducing the TTM while simultaneously considering in inherit uncertainty of the clinical trials. With this literature review, RQ2 has been addressed. In the next section, observations from the case study are stated, which highlights the challenges in reducing the TTM and thereby shows a way for finding new methods to reduce the TTM.

Insights from the Case Study

All interviewees pointed to the clinical trials as being the major bottleneck for the whole new product introduction process. The reason was that trying the drugs out on patients, finding and analysing the results is simply a lengthy task. During the interviews the managers were inquired about the current planning techniques used by the company to plan the clinical trials while considering the entire pipeline. The interviews revealed a simplistic and pragmatic approach to decision making, which consisted of identifying key figures, discussing risk elements and making gut feeling decisions of which drugs to allocate which resources for.

Observation 1: Risk elements seem to be handled with gut feeling and simple measures at best. No consistent methodology is employed for pipeline management.

Whereas the available planning techniques for the pharmaceutical industry have evolved in the literature during the last 10-20 years, it seems the industry has been slow to follow. More focus should be given to the implementation of such techniques.

In the case company, the Market Access section was involved early in the new product introduction process as advisors. The reason for this was in part so that they could start preparing the sales organisation for the launch, but they were also used as consultants in setting up the clinical trials. Different authorities in different countries demand different tests and documentation to grant their approval. The decision of whether to do certain trials up front to gain faster approval or whether to do these later and get the drug out onto a smaller number of markets fast is not trivial. To the best of our knowledge this has not yet been mentioned in the literature.

Observation 2: There is no or little attention given to how market expansions and clinical trials should be planned simultaneously and what the effect is on the time-to-market.

So far only the two most central regulatory authorities have been mentioned, FDA and EMEA, but there are many more. In Europe only the approval can be granted through the centralised system administrated by EMEA. For negotiating a subsidy, the company has to carry out separate negotiations with each member country or possibly each municipality. This leaves a lot of negotiations to be carried out. The order in which these negotiations are carried out is decided based on a business case made by the company, which considers authority requirements, potential market size, potential subsidy and expected negotiation time. As different authorities use different techniques for awarding or evaluating subsidies e.g. comparison to other countries or based on production cost, the order in which these subsidy negotiations are carried out influence the overall granted level of subsidies. A higher subsidy leads to higher potential price of the drug and increased sales i.e. higher revenue. This creates a trade-off between scheduling negotiations to either obtain higher subsidies or to schedule negotiations such that markets can quickly be accessed. Again, the process of scheduling market access negotiations was described as being based on gut felling decisions.

Observation 3: A systematic approach to address the trade-off between negotiating for a higher subsidy versus negotiating for a faster market introduction seems to be missing.

In preparation for the launch of a new drug in a market, it is industry practice to build up stock to get the drug to the customers as fast as possible. Here planning for worst case scenario is widely used. However due to the poor accuracy of forecasts, even planning for a scenario based on optimistic sales scenarios may not be enough to assure sufficient availability. Since the last part of the approval process often involves changes to the label on the package, drugs are normally not packaged before the final approval is granted as repacking is not allowed by the authorities. The decision whether to package the dug up front despite the risk or ‘risk packing’ offers the trade-off between potentially saving the packaging procedure after approval and reduce the step between approval and launch versus the risk of having to change the label and throw away the entire packaged inventory. Throwing the drug away is not only expensive but leads to a further delay of the launch if the product has be produced again.

Observation 4: Inventory sizing and production start up for launch is not addressed in the literature. No appropriate method for assessing risk packaging has been found.

From the observations made above, it seems that the two predominate ways of reducing the TTM. The first is to balance the planning of clinical trials with market access planning simultaneously. The second is to focus on planning related to the phase between approval and launch, where either the order of the subsidy negotiations or level of risk packing can impact TTM positively. With this conclusion, RQ3 has been answered.

Conclusion

In this contribution the new product introduction process in the pharmaceutical industry is studied. A project network was created in a case study followed by a precedence relationship. The literature was reviewed, but no real contribution in reducing time-to-market for the industry was found. A series of observations were made, which ended with an identification of the key areas were focus should be put in the future.

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