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Resource Management in an Industry with Long-term Return – Increasing Efficiency Along the Pharmaceutical Value Chain

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Ph.D. dissertation

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1. Introduction

1.1 Exposition

The present dissertation is an investigation of how efficiency can be increased, and resources optimally managed, in the pharmaceutical industry, in which the core business is capital intensive and is characterized by a high *time-to-market* (TTM) (e.g. Pawar et al. [1994], Smith [2004]) and long-term returns. As most pharmaceuticals are not purchased out-of-pocket by patients but are rather provided to them by national health systems or social security schemes, the long-term return is heavily dependent on the actual status of the regulatory and reimbursement environment in the key sub-segments of the global pharmaceutical market (Mossalios et al. [2004]).

The pharmaceutical industry is characterized by the following:

- it is in fact not one industry, but rather a set of industries with different business logics;
- the technological decisions made at the beginning of the product life-cycle have long-term effects on later production development options and, indirectly, also on the profitability of products, that is to say they cause partial – or less frequently complete – *technological path dependence* (see e.g. Liebowitz-Margolis [1995], Arthur [1989]);
- during the protracted product development process, the risk associated with the technological feasibility, regulatory compliance and business viability of the product can only be reduced in a number of consecutive steps (*multistep risk management*), with a number of *stop-or-go* decisions having to be made while the *psychological commitment* of participants increases in proportion to the quantity of effort and capital invested, which may become a factor causing inflexibility and hence a risk factor in some cases (see e.g. Brockner [1992, Staw [1981]);
- besides business considerations, ethical aspects also have a key role in product development, and these two viewpoints may become conflicting (Sloan-Hsieh [2007]);

- during the product life-cycle, people from a number of different professions (specialists in the natural and life sciences, technologists, economists, lawyers as well as other professions) contribute both individually and as members of *multidisciplinary* working groups – the latter lending particular significance to organizational coordinatory endeavours, which, of course, also increases *coordination needs and costs* (see e.g. Dobák [2006], Niehans [1987]).

In the light of all of those factors it seems logical, both theoretically and in practice, to implement the following guidelines:

1. firstly, in order to use available resources efficiently, work organization methods, innovation management, technology management and process management tools, public affairs and lobbying efforts, marketing tools, production technology solutions and management control tools should be used in a coordinated, mutually complementary manner, but with shifting emphasis along the product life-cycle;
2. secondly, the actual status and potential changes in the regulatory and reimbursement landscape must always be taken into consideration in the key markets, and efforts should be carried out to influence these changes in a way which is beneficial from a business perspective;
3. thirdly, the multiplicity of tools and solutions associated with the various professions and approaches, and their mutual interdependency, which is highly significant factor for success demand an integrated, comprehensive approach that transcends the traditional constraints of the individual professions. From a somewhat reversed perspective this means that efforts aimed at optimal resource allocation may only be successful if a management approach that transcends individual professions is 'institutionalised' and becomes an integral part of the organization's decision-making process.

We may also assume that the various solutions aimed at improving efficiency vary in significance and have varying effects on business success, i.e. they vary in potential. An improvement of efficiency in pharmaceutical development, for instance, will have positive effects throughout the life-cycle of the project as it allows the drug to reach the market earlier, while the reorganisation of warehousing tasks will only affect a small slice of the total cost. Finally, we may also make the assumption that in the pharmaceutical industry, as elsewhere, the success of initiatives aimed at developing

efficiency depends on the existence of appropriate organisational mechanism and the degree of integration into organisational decision-making – in a single word, on implementation.

The objective of my dissertation is to examine the solutions used for improving efficiency in the various segments of the pharmaceutical industry and to assess their relevance.

1.2 Antecedents of the dissertation, related other research

I intend my dissertation to fit into the series of doctoral dissertations that constitute the results of the academic research conducted at the Institute of Management of the Corvinus University of Budapest, while at the same time reflecting upon the clear shift in my research interests in the past couple of years. The Institute has established two definitive directions of research that the present dissertation is closely related to and whose previous results it can hence make use of while, hopefully, it will also make a contribution to the scientific achievements of the Institute.

- One of those research areas is concerned with the development and Hungarian applications of the toolkits and methods of performance management. Within that field of research, in addition to the work conducted in the 1990's that had laid the foundations of the field, (e.g. Horváth-Dobák [1993]), I should particularly mention the doctoral theses of Viktória Bodnár and László Lázár (Bodnár [1999], Lázár [2002]) which provide wide-ranging summaries about the fields of controlling and cost mapping and the publications and conference papers that have attempted, in recent years, to resolve the conceptual chaos that characterizes the discipline of controlling (see e.g. Bodnár [2005, 2007], Bodnár-Dankó [2005], Dankó [2005], Harangozó [2007]).
- The other direction of research, which has come to be one of the central fields of research for the Institute, is healthcare management and healthcare controlling, in which recent years have seen several publications and conference papers by Viktória Bodnár, Dávid Dankó, György Drótos, Norbert Kiss, Márk Péter Molnár, Éva Révész, Csilla Varga-Polyák and others. That research has covered the micro-level (institutions), the middle level (networks) and the macro-level (public policy,

sectoral level performance management) of the healthcare sector as well. It was within this research stream that a sub-stream focused on pricing and reimbursement as well as market access issues in the pharmaceutical industry. This sub-stream is mostly represented by research and publications by Márk Péter Molnár and myself, not independently from our previous practical experiences.

During the compilation of my dissertation, I endeavoured to build on all the experience I gained during my diploma research project that was initially published as an article (Dankó [2003]), the subsequent assignments as an expert in the pharmaceutical industry, the role I then came to occupy in relation to decision-making and analyses associated with drugs and finally the joint research and projects I conducted with pharmaceutical companies. During the time of writing, I found myself in a somewhat awkward situation: by the time I had defended by draft dissertation, my practical work had moved me closer to the issues of reimbursement policy, i.e. it so happened that my knowledge of the issues that are the subject matter of the present dissertation gained greater clarity and detail not from the perspective of the pharmaceutical industry but from the side of the regulator and payer (the "other side"). As a result, while I would clearly have a comparative advantage if I were submitting a dissertation about reimbursement policy, with my actual subject I can only hope that I was able to augment my experience of the "other side" with the additional research and the closely connected expert work I performed after I stopped working for payer organizations so as to achieve a dissertation that is relevant and valuable.

1.3 Use of concepts and choice of industry

1.3.1 About the use of concepts

The scientific terminology of the social sciences, and within them management sciences, which are themselves applied disciplines, is in a constant flux. In addition to deeper trends, the terminology also exhibits periodic superficial fads (see, for instance, the seminal article by Abrahamson [1996]). The present dissertation – while accepting that continuous changes in terminology are inherent to science – does not aim or intend to take a stand on issues of terminology related to its subject or to attempt to resolve any terminological ambiguities. Nevertheless, it should be taken into account

that the multidisciplinary nature of the subject of this dissertation, together with its sociocultural embeddedness, severely constrains, or practically rules out, any precise and consistent use of terminology. We are inevitably confronted with the fact that the representatives of various professions and scientific fields use different concepts and specialist terms to describe similar phenomena. For instance, in place of the term *core process optimisation*, which has a 'management-scientizing' feel to it, an engineer may talk of *production technology development*, while a chemical technologist may mention *process chemistry*, but all three of them would have roughly the same thing in mind. Secondly, the use of precise concepts is problematic in relation to the subject of the present dissertation even if we remain within the limits of management sciences.

Based on the dichotomy anecdotically attributed to Peter Drucker (Drucker [1993]), my dissertation places the focus not on the external component of the success of organisations (*effectivness*) but, rather, on the internal component, efficiency, which, to put it simply, means achieving the maximum result with a unit or resources. In the final analysis, developing the efficiency of the functioning of an organisation means approximating the most rational management of the various available *resources*, while the *resources* themselves – in line with Barney's [1991] interpretation – are the material and non-material things that are available to the organisation, that the organisation has the right to dispose over. Accordingly, I shall use the neutral, clearly intelligible term "*resource management*", which also appears frequently in the literature, as the central concept for the purposes of my dissertation: under my interpretation, every conscious effort aimed at improving the efficiency of the organisation, as well as all supporting methodologies constitute resource management. Resource management includes and synthesises, among others, the elements of cost management, process management, risk management, quality management, information management and project management. (A more extensive exposition of the concept of resource management is provided in *Chapter 2*.)

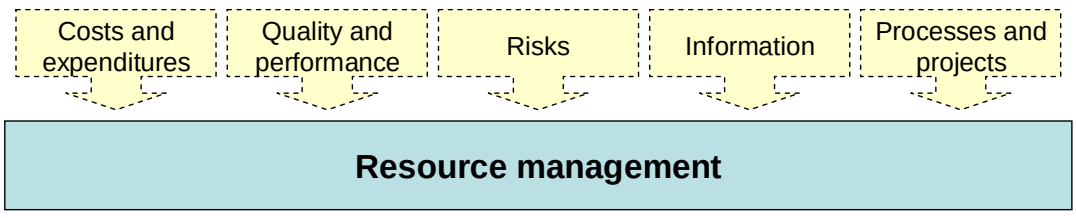

Figure 1: Resource management as an integrative notion in this dissertation

It must be emphasized, however, that each specialist term has serious arguments both in favour of and against it. *Resource management* is no exception. In all probability, for other researchers it is the term *performance management* (or efficiency management or process management) that has the conceptual clarity that I intend to ensure through using the term *resource management* in my dissertation. A few years ago, a thorough description, explanation and comparison of those terms could have been a subject for a separate dissertation in themselves. One of the critiques of my draft dissertation has indeed mentioned that I had failed to provide an exact definition and exposition of resource management – yet the literature I have read and all the thinking I did during the intervening period have still failed to provide an answer I found satisfactory, so in the final version of my dissertation I am still forced to apply some simplifications, although, relative to the draft, I have refined my conceptual apparatus significantly.

So, while I recognise that any use of concepts is open to debate, in my defence I would like to refer to the clear limitations of length and also contend that while these dilemmas may constitute relevant research questions for those in management science, they are irrelevant for the specialists working in pharmaceutical development and marketing as well as the scientists studying those fields in other branches of science. In those branches of science, other terminologies are in use, while a collective concept is as yet missing. That is why I tried to chose a term to be the central keyword of my dissertation that is intelligible to those working in other fields – and the best candidate based on that criterion was “resource management”.

1.3.2 About the choice of industry

The pharmaceutical industry is complex: drug companies exhibit all the essential characteristics of industries with long-term return *in a concentrated fashion*. What’s more, the pharmaceutical industry is not even really a single industry but the composite of at least three different sub-industries (segments) – a claim that I shall support at greater length below (Gassmann et al. [2008] pp. 20-22). As a result, the pharmaceutical industry is a sector that is an inexhaustible source of subject matter for scientific

research whose results, with the appropriate adjustments, can also be transferred to other – mostly less complex – industries.

It is a further objective argument in favour of the pharmaceutical industry that to the best of my knowledge, nobody has investigated the issues of long-term resource management in the pharmaceutical industry in Hungary to date. Even the international literature features only a very few publications that approach the pharmaceutical industry from this perspective:

- Most non-medical articles approach drugs through issues associated with health economics and technology assessment, and with a methodology focus. Articles of varying length, attitude and rhetoric ponder the conundrum of reforming the financially increasingly unsustainable drug reimbursement schemes of the welfare societies without jeopardizing patient care or resulting in a socially unacceptable situation. The 'scientific market' of the field can be considered to have matured and boasts several high-prestige, frequently referenced periodicals (e.g. *Health Economics*, *Journal of Health Economics*, *European Journal of Health Economics*, *Pharmacoeconomics*), research centres and specialist literature.
- The medical and non-medical (partly management-science and partly engineering-related) literature of pharmaceutical research and development and associated technological innovation is also significant. A number of journals are devoted to the subject (e.g. *Scrip*, *Drug Discovery Today*, *Pharmaceutical Medicine*, *Journal of Pharmaceutical Sciences*). The organizations of pharmaceutical R&D companies also issue regular publications in which they present the development of pharmaceutical technology and stress the time- and resource-intensive nature and complexity of drug development.

On the other hand, resource management in the pharmaceutical industry as a field of scientific research has largely remained uninvestigated. The primary reason, presumably, is constituted by confidentiality issues. The complexity of the industry, which results in a business administration approach yielding only partial results, also has a role. Finally, studies are predominantly prepared by consulting firms and are sold at exorbitant prices despite their varying quality.

I have identified five main factors of complexity from the perspective of the management sciences:

1. The pharmaceutical industry is not a single industry but the totality of sub-industries that follow different strategy models. The individual sub-industries exhibit completely different behaviour and exist in a complex set of substitutional and competitive relationships.
2. The pharmaceutical industry is a resource-intensive, high-tech industry with very significant spending on research and development. The technologies used are highly specialized, projects are complex and usually extend over long periods of time. Risks are also exceptionally high and minimizing them requires the cooperation of many professions and specialist fields.
3. The pharmaceutical industry is a 'regulation-intensive' industry. Firstly, it is no exaggeration to say that it has been legislated into the ground, which is, of course, understandable. The authorities subject the development, testing and manufacture of drugs to strict requirements so as to ensure perfect drug safety in order to protect human health. Secondly, the pharmaceutical industry is also a veritable jungle of product and process patents, the 'heartland' of patent litigation. Thirdly, the majority of modern drugs are only able to reach the market because the financers pay a significant part of the price of the drugs instead of the patients. They do so, however, with a severe set of conditions attached, which have a fundamental effect on the market profitability and competitiveness of drugs.
4. Capital allocation decisions concern huge amounts and despite the highly research-driven nature of the industry those decisions have recently come to be made increasingly on the basis of strategic and marketing criteria. The pharmaceutical industry is characterized by a mixture of resource-based strategies and long-term, proactive marketing work[1].
5. Information is often highly valuable and hence kept secret in the pharmaceutical industry. Competition is so heavy, main avenues of action are so parallel and the approaches and objectives of individual companies are so similar that the leaking of information can cause enormous damage to any particular company. With the

exception of long-term strategic or occasional cooperation (e.g. lobbying), the companies usually treat all internal (production and business) information confidentially and they handle information with great care even when they do cooperate.

All of those factors make it difficult to produce a piece of work that addresses resource-management issues in the pharmaceutical industry from the perspective of management sciences. One particular difficulty is that the required information is only available in the literature in small fragments scattered around various books and articles in many periodicals. I am only aware of comprehensive monographs about the management of drug research and the innovation process – and I shall refer to those in my dissertation. I can only attempt to overcome those difficulties in my thesis.

1.4 Research questions and hypotheses

In accordance with the above considerations, in my PhD dissertation I shall examine the solutions that companies in the original and generic pharmaceutical industries use in the pharmaceutical value chains in order to improve their organisational efficiency. My basic assumption for conducting that study shall be that in the pharmaceutical industry, the optimisation of resource allocation is implemented partly in the fundamental processes (using *scientific and technological solutions*), partly through *work organisation solutions*, and partly by using *business tools*, and the relevance of the various types of tools varies in the individual value-chain sections as well as between the different strategic models of the pharmaceutical industry (for more detail, see *Section 4.1*). The variation in relevance is the result of differences in potential and implementability. In my research, I shall study *perceived* relevance throughout – the subjective significance that specialists in the pharmaceutical industry attribute to the solutions in question.

[1] The nature of the objectives of pharmaceutical companies is the subject of many barren disputes in which the conflicting positions are usually motivated by interest, emotion or ideology. Yet the answer is trivial: the pharmaceutical industry is driven by money just as all other industries are, and just like in those, decisions are based on criteria of profitability. The pharmaceutical industry is neither more, nor less ethical than other industries, it simply has different characteristics and through the topic of human health and life it is more of a focus of public attention.

In the rest of my dissertation I shall study the following research questions and corresponding summary hypotheses:

Research question	Summary hypothesis
1. What are the solutions available for increasing efficiency in the various sections of the original prescription only (ORX) and generic prescription only (GRX) value chains?	*This research question is aimed at gathering information, so it does not have any corresponding summary hypotheses*
2. What is the relative (perceived) relevance of those solutions along the individual value chains?	H1. In the preclinical phase of the value chains, scientific and technological solutions have the greatest perceived relevance, with work organisation tools in second place and business tools coming last. H2. In the clinical phase of the value chains, the perceived relevance of scientific and technological solutions decreases while that of work organisation solutions and business tools increases. H3. After going to market, business tools assume the dominant role in both value chains.
3. What are the main differences between the resource-management tools used in the original prescription only (ORX) and the generic prescription only (GRX) business models?	H4: In the generic prescription only (GRX) business model, the perceived relevance of business tools lags behind that of scientific and technological solutions and work organisation solutions to a lesser extent than in the original prescription only (ORX) model. H5: Resource management after the product is placed in the market is more significant in the generic prescription only (GRX) business model than in the original prescription only (ORX) model.

Table 1: Research questions and corresponding summary hypotheses of the dissertation

A more detailed description of the analytical framework, the research questions and the summary hypotheses are presented in *Chapter 4*. However, it is important to emphasise here that the primary purpose of my dissertation was the creation of a taxonomy. There is only fragmented information available, the overall picture is underdocumented in the literature, while the opportunities for quantitative research are rather limited due to the character of the subject (see the *next subsection*). As a result, the study that matches the questions being asked is primarily inductive: a review of the theme and the matching up of the various details give rise to the documented and

structured overview that may represent the added value of the research work. In consequence, the emphasis will be placed on the research questions, they will be more significant relative to the hypotheses. The hypotheses themselves only furnish possible answers and are unavoidably partial. Their role was that I could build on them to prepare for the in-depth interviews and they also served as the compass for the supplementary secondary research.

I believe it is important to note that the specific research questions have been greatly refined relative to those featured in the draft dissertation, and the emphasis was also placed elsewhere. The primary reason for that is that my reviewers were unanimous in noting the insufficiently considered character of the questions, and I attempted to take that rightful criticism to heart.

1.5 Research approach

As regards its basic epistemological orientation, my dissertation remains within the framework of *functionalist sociology* (Burrell-Morgan [1979]), i.e. I shall assume that I can *obtain objective knowledge* about my research subject. In relation to that, as an observer I shall remain outside the subject matter of my thesis: I shall attempt to map and interpret reality as an *external observer*.

My dissertation does not have a normative or critical intent, but it does aim to describe, explain and *organize* the phenomena within its subject area as thoroughly as possible. It aims to integrate inasmuch as it wishes to facilitate integration between fields of science that traditionally have little contact and that it identifies with the multidisciplinary approach. The underlying attitude behind the systemic approach and the integrative intent is an admittedly *contingentialist* one (see e.g. Dobák et al. [2006], Kieser [2003]) towards research, characterized by the view that environmental and contextual factors have a fundamental effect on the structural and other operational characteristics of organizations and the coordination tools that they use, including the tools, methods and mechanisms of resource management.

In addition to the systemic approach with contigentialist foundations, I intend the above-mentioned *multidisciplinary perspective* to be perhaps the most important

distinguishing feature of the dissertation. As a researcher, I am convinced that people doing theoretical and practical work in the management sciences can improve their chances of reaching new insights, developing innovative solutions and addressing the problems of organizational life in a manner befitting their weight if they have some understanding of the technical and natural scientific background of the core processes. In general, achieving such an understanding is not very difficult, though it does require time and receptivity. I have made the assumption that the target audience of my dissertation does require such an understanding even at the cost of receiving only a more concise and superficial analysis of certain management problems due to considerations of length.

I have aimed to produce a dissertation that complies with the standards of form and content generally adopted by the scientific community while remaining *easily comprehensible* for a wider public. This concerns, in particular:

- the language I adopt, which for the choice of subject cannot entirely avoid the use of specialist and scientific terms primarily but still strives to avoid any arbitrary use of unnecessary jargon;
- the means of drawing scientific conclusions, which shall be verbal, i.e. my disposition shall be almost entirely devoid of mathematical and logical formalism;
- the structure of the text, to the extent that I shall endeavour to present linear trains of thought and to divide chapters into sections for the sake of clarity, employing figures and other devices aimed at facilitating understanding as I see fit.

1.6 Methods of analysis

In line with the research approach, the *methods of analysis* shall be as follows:

- The chapters outlining the basics of resource management and the general description of the pharmaceutical industry (*Chapters 2 and 3*) are based on a detailed and extensive *review of the literature* that covered the major periodicals in the management sciences, pharmaceutical research, technology and chemical technology. Secondly, the literature review also included the specialist books on the subject that are available to me, largely about general issues of management,

innovation and production organization in the pharmaceutical industry.[2] The review of the literature was already a part my draft dissertation, but, in accordance with the suggestions of my reviewers, I have made the parts summarising theory somewhat simpler.

- Based on the detailed literature review, the experience of the previous research efforts mentioned in *Section 1.2* and background interviews conducted with pharmaceutical specialists I performed *independent scientific differentiation* to arrive at the analytical framework of the draft dissertation (*Chapter 4*), which, firstly, attempts to integrate the theory of resource management with the operational characteristics of the pharmaceutical industry, secondly, it foreshadows the logic of the empirical research section of the dissertation and thirdly, it renders the research questions of the empirical study more specific. The analytical model has become somewhat simpler relative to my draft dissertation.
- The reviewers of my draft dissertation had several critical comments to offer concerning the planned methodology of the empirical study. The most important one was that the research questions I had outlined were highly unlikely to be answered with sufficient certainty by a study limited to Hungary only, as the relevant decisions and activities take place at corporate headquarters outside Hungary. My reviewers also emphasised that while the research questions need to be formulated with greater accuracy, the sample I selected would still not be suitable for drawing valid conclusions. Accepting their advice and suggestions I performed a radical reconsideration of the research methodology: firstly, I gave up the notion of limiting the study to Hungary only and I attempted to find international sources of information; secondly, I also decided to not use questionnaires with questions requiring descriptive responses, as the conceptual complexity of the theme would have made my questions difficult to comprehend for my research subjects representing various professions and levels of decision-making, and I decided to use only in-depth interviews instead. Thirdly, I also used secondary sources in relation to areas and questions to which my interview subjects themselves were unable to provide information directly, but were able to point me to case studies in the literature that I felt were relevant. Fourthly, I also relied on personal

[2] The literature I reviewed is presented in full detail in the *List of References*. For ease of use, the List of References includes the works related to the introduction and the theoretical background of resource management on the one hand and those related to the general description of the pharmaceutical industry and resource-management in the pharmaceutical industry on the other hand in two separate sections.

communications I received from the executives of international pharmaceutical companies when my work or my attendance of conferences afforded opportunities to talk to them; I emphasise that those conversations were not scientific in character and they cannot be considered to be parts of my research, but they are highly significant for the subject of my research. All in all, I used a methodology with three basic pillars: I conducted in-depth interviews with specialists who have experience of the international decision-making levels and mechanisms associated with the marketing of pharmaceutical drugs and I supplemented that with the literature – largely case studies – they suggested and I also used some information communicated in informal discussions outside the scope of the actual research.

The complexity of the subject matter of my dissertation, the multidisciplinary approach and the difficulties of accessing data imply several types of *risk*, and the limitations of length are also rather strict. Notwithstanding this, I remain confident that the multidisciplinary approach and the research methodology I have adopted are suitable for interpreting the phenomena to be examined and for reaching at scientifically valid inferences.

1.7 Structure of the dissertation

After the present Introduction, my dissertation shall have the following structure:

- In *Chapter 2*, I shall review the theoretical background of resource management briefly and, based on the possible interpretations and approaches I shall formulate a definition for the purposes of the present dissertation that I judge to be consistent with the characteristics of industries with long-term return, and specifically the pharmaceutical industry.
- In *Chapter 3*, which shall address a mixture of market, technological and pharmacological factors, I shall provide an overview of drugs, their production and the pharmaceutical industry itself. I shall discuss specific issues of the pharma industry at relative length because I believe that without that supplementary information it is not possible to define the boundary conditions of resource management in the pharmaceutical industry exactly.
- In *Chapter 4*, I shall present the theoretical background for the empirical study outlined through my own scientific classification work, the research questions and the research methodology.

- *Chapter 5* outlines the results from my research along the hypotheses I formulated.
- *Chapter 6* contains some conclusions I feel can be regarded as the main value-added of my research.
- This dissertation comprises an *Appendix*, a detailed *List of References* and a *list* of the author's previous publications about the subject.

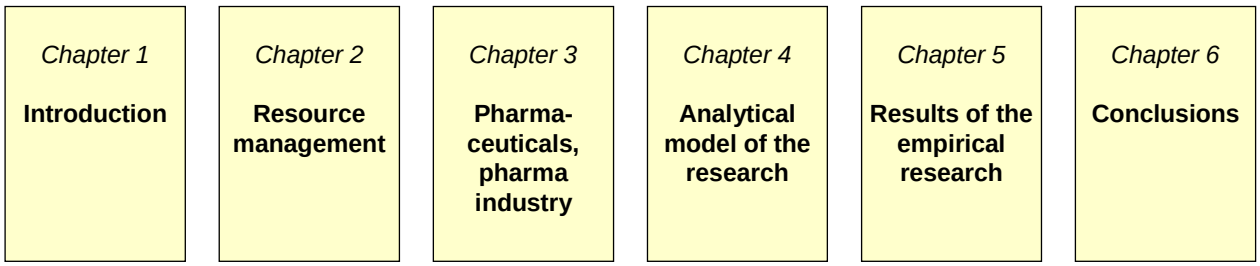

Figure 2: Structure of the dissertation

1.8 Acknowledgements

I consider myself fortunate in the sense that in my present position as well as in my previous one, my scientific and practical work has furnished opportunities for discussions and cooperation with a number of excellent specialists working in the pharmaceutical industry or in adjoining industries and the associated parts of the public sector. I was able to understand the ways of thinking of several professions, segments of the pharmaceutical industry and stakeholder groups with their help.

I would like to express my gratitude to my colleagues at the Institute of Management at the Corvinus University of Budapest for their support, encouragement and valuable discussions. I would particularly like to thank professors Miklós Dobák, László Lázár, Viktória Bodnár and Sándor Takács for their direction, their useful advice and for bolstering my strength during the inevitable spells of desperation. I also thank Márk Péter Molnár for refining, both as a friend and as a colleague, many of the ideas contained in this dissertation.

I dedicate my dissertation to the memory of professor Sándor Kovács: if he were still with us today, he would probably tear my thesis apart, but only to make it much better with his criticism.

2. Resource management

2.1 The necessity of interpreting concepts

My first task is to clarify what I understand resource management to be for the purposes of the present dissertation and to present a possible interpretation of the concept that matches well the characteristics of industries with long-term return, and specifically the pharmaceutical industry. Naturally, due to the essential features of management sciences themselves, my interpretation is only a single, *subjective* interpretation among a great many. As such, it is closer to the opinions of some while it is more distant from the opinions of others. Nevertheless, I hope that I shall succeed in outlining an approach that is at least defensible and which allows the essential points of my dissertation to be assessed within the framework of endogenous criticism.

Essentially, my interpretation is not a new one, it is rather an amalgamation of the interpretations I have found in the specialist literature and in neighbouring disciplines. I felt it was important to take the latter – research conducted by consultants, information material from management services, the revelations of 'management gurus', etc. – into account because scientific (academic) results concerning resource management largely reach end-users, i.e. the various level executives of corporations, through those mediators. From the perspective of science, those neighbouring areas represent the 'noise' that usually only allows original ideas to reach their target audience in a distorted, usually greatly simplified form, but from the perspective of that target audience, complex scientific results only acquire practical utility or indeed become comprehensible at all through the practical interpretations of those neighbouring fields. This implies that the role of those intermediate areas is considerable from both perspectives.

After providing a working definition for the terms 'resources' and 'management', I shall review a variety of *culturally different approaches* to resource management at somewhat

greater length below. I shall present four main trends, dividing them into sub-trends where necessary and possible. Those four trends are the German, the Anglo-Saxon, the Japanese and the Scandinavian schools, with sub-trends distinguishable within the first two, the German and the Anglo-Saxon schools which both have rich literatures. Of course, the weight, currency and level of acceptance of the schools and sub-trends vary, to a large extent due to the current Anglo-Saxon hegemony in management sciences (see e.g. Alvesson-Willmott [2002]). For instance, Japanese ideas concerning resource management have reached the western world almost exclusively through American intermediaries and at most half a dozen Japanese professors who also write in English, which has inevitably resulted in the loss of some important features (Cooper [1995]). On the other hand, it is only a slightly cynical claim that the Scandinavian school is only considered an independent trend by Scandinavians themselves.

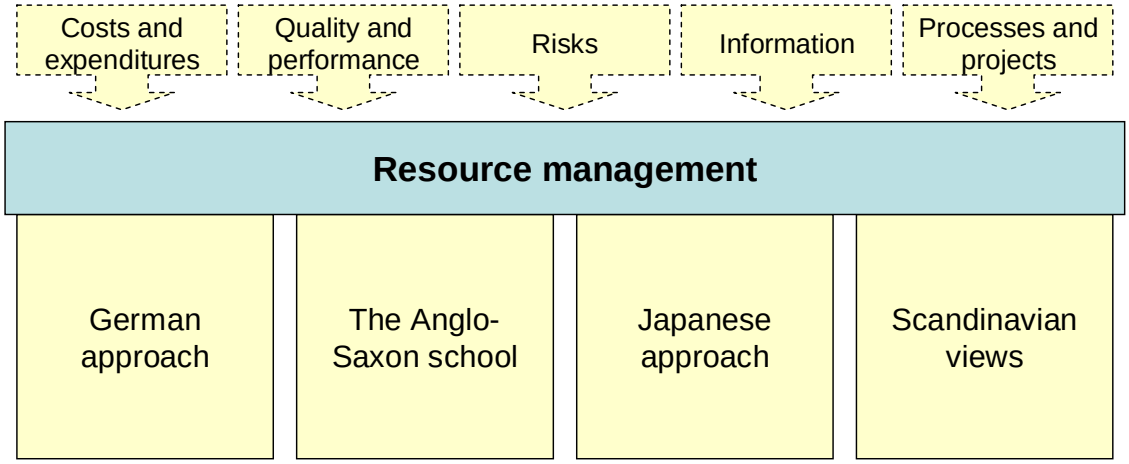

Figure 3: Different cultural approaches to resource management

Due to limitations of length and the ample availability of corresponding literature, I shall not discuss the subdisciplines of management sciences that may provide methods or approaches for the definition of the thing that I refer to as resource management in line with the argument presented in Section 1.3.1. For expositions of those concepts see e.g. Drury [2007], Brealey-Myers [2005], Iványi-Hoffer [2004], Chikán [2002], Görög [2001] and Kaplan-Atkinson [1998]).

2.2 Possible interpretations of and approaches to resource management

2.2.1 Resources and management

In the terminology I follow in my dissertation, resources are all tangible and intangible assets that are at the disposal of an organization and which the organization has the right to use (see e.g. Barney [1991]). Resources include assets acknowledged as such by traditional accounting standards, but also intangible goods such as intellectual and infrastructural capital, managerial competences, organizational climate and culture, brands etc. For any business organization, resources can particularly be a driver of success when they are valuable, rare, inimitable and non-substitutable. These criteria – of which the latter two are the foremost pillars of long-term competitiveness – are commonly referred to as VRIN, an acronym formed from the initial letters of the respective adjectives (Barney [1991]).

Management may stand for directing, leading or organizing, depending on different contexts (see e.g. Dobák [2006]). For this dissertation, I shall rely on Drucker's [1993] approach which states that management is a conscious role and activity of organizing and directing with the aim of ensuring the efficiency and effectiveness of work, supported by institutionalised systems within the organization (Drucker [1993] pp.40-42).

2.2.2 The German approach

Germany has a long tradition of thought concerning resources and resource management, a fact that is attributed by many to cultural reasons that can be summarized at the cost of some simplification as 'German precision' (Nehler [2001] pp.23-26). It is certainly true that in the German cultural sphere, there is a traditionally strong emphasis on the *efficient* management of resources, whereas in the Anglo-Saxon culture, resource management (i.e. costs) were looked upon for a long time as something that is not particularly important as long as the product is possible to sell with the profit margin initially imagined.

'The views of German manufacturers are very different in this respect to those of British ones. The Brit [...] asks this question: what turnover do I need to realize in order to realize a certain percentage profit on top of the prevailing production costs while also covering the costs mentioned previously [overheads –

D.D.], and then, all he cares about is the turnover. In our country, the manufacturer starts from completely different principles. He wishes to allocate the appropriate part of the overheads to each piece of work (...)' (Strousberg [1876] p. 413, quoted by Seicht [1997], p. 282, *translation by the author).*

'The American practice [of cost calculation] is characterized by very strong pragmatism. That is why Americans are sometimes referred to as "cost managers", while Europeans, who primarily speak German, are better described by the term "cost engineer". In another sense, those differences manifest in relation to precision and the depth of analysis [...])' (Nadig [2000] p. 10, *translation by the author*).

It may also be the result of the difference in habits of thinking that in Germany the notion of tracking the resources consumed and to be consumed in order to manufacture products and the distinction between costs arising due to the products (today called direct costs) and those arising independently of the products (today called indirect costs) already arose in Germany at the end of the 19th century. As early as 1899, Schmalenbach, for instance, wrote that only those costs (*primäre Unkosten*) should be allocated to products that arise directly in relation to their manufacture – whereas all other costs (*sekundäre Unkosten*) should be covered by 'raw profit' (*Rohgewinn*) (Seicht [1997] p. 283). Schmalenbach was also the first to arrive at the thesis (in 1919) that when constrained capacities are utilized, the correct foundation for pricing is the marginal utility produced by a unit of those constrained capacities (Seicht [1997] p. 283).

From there, there was practically a straight road towards the development of German management accounting (*betriebswirtschaftliches Rechnungswesen*) that considers the supporting of corporate decisions with actual figures – in other words, an emphasis on relevant resources and their consumption – to be at least as important as calculation and contribution calculations. The most important authors that played a part in shaping that trajectory of development – including Schmalenbach, Kosiol, Rummel, Plaut, Agthe and Mellerowicz, Riebel, Kilger, Laßmann and others (for more details, see e.g. Coenenberg [2003], Lázár [2002], Schehl [2004]) – used their models of varying practical utility to turn German management accounting into an increasingly decision-oriented discipline, but the modes actually accepted in practice largely retained the functional (divisional) calculation algorithms of the traditional approach. With some exaggeration, the developers of those models were more interested in defining the range of relevant

resources and costs than in what happened to them in the course of actual calculations[3]. On the other hand, the methods that partly or wholly broke with the traditional functional thinking were not really applied in practice and today they are largely considered intellectual curiosities. Several people attribute this to their excessive sophistication (Kloock-Sieben-Schildbach [1999], Mayer [1998]).

That duality – namely that quantitative decision support increasingly became the primary objective of management accounting while the methods it employed changed very little – also had the effect that the terms 'management accounting' (*Betriebsrechnung*) and 'cost accounting' (*Kostenrechnung*) have remained suitable collective terms until very recently. At most, they were accompanied by the qualifying terms 'decision-oriented' (*entscheidungsorientiert*) or 'concerning the future' (*zukunftsbezogen*) in order to distinguish them from classical costing. The terms 'cost management' (*Kostenmanagement*) and 'resource management' (*Ressourcenmanagement*) were almost entirely unknown in the German literature until the end of the 1980's and the latter has remained rather rare to date.

The arrival of activity and process-based approaches, in particular, process-oriented costing (*Prozesskostenrechnung*) at the turn of the 1980's and 90's seemed to bring a breath of fresh air in several respects. It has been established that process-based costing had existed earlier (Horváth-Mayer [1995] p.59), but it is indisputable that the methodology only matured about that time. The American 'discovery' of activity-based thinking (e.g. *Activity-Based Costing* – ABC) and the profit-oriented consultancy firms that promoted the new ideas and often packaged them with other procedures (e.g. *Target Costing*) played a large part in the process of maturation. Presumably not independently of the influence of consultants, process costing soon grew into cost management and process management, with increased emphasis on purposeful 'resource management' in the German literature[4].

[3] For the seminal authors of the German school of management accounting, see Mayer [1998], Coenenberg [2003], Seicht [1997] and Schehl [1994].

[4] For more information about process costing, and more generally about the German interpretation of process-based thinking, see the works of Coners-von der Hardt [2004], Coenenberg [2003], Coners [2003], Gaiser [1998], Wüest [1996], Horváth-Mayer [1995] and Küting-Lorson [1995].

The new rhetoric and approach had its fair share of critics and opponents. The committed protectors of decision-oriented management accounting – for instance Seicht, or the more 'moderate' Schildbach – described process management, cost management and the movement that used them as its defining terms as a vulgarisation of knowledge that had been available for a long time and either commented rather sarcastically on them (Kloock-Sieben-Schildbach [1999] p.236), or attacked them vigorously (Seicht [1997] pp.562-576). T hat school, which I shall refer to as the 'conservatives', sees cost and process management as a fad and accuse them of an intention to undermine an ancient principle, the 'indivisibility of accounting'. According to the conservatives, the drive towards proactivity, which lends their confidence to the spreading new gospels of management, had already been present within decision-oriented management accounting (Seicht [1997] p.565).

Other scientists and professors, e.g. Coenenberg [2003] and Kloock [1995] are understanding towards cost and process management, indeed, some of them – for instance Gaiser [1998] and Horváth and Mayer [1995] – have become its pioneers. They (the 'moderns') criticize the conservatives for their inability to overcome their functional, accounting-based approach and for their excessively rigid adherence to the thesis that traditional accounting is capable of meeting all the demands of business executives (see e.g. Mayer [1998]). The moderns make much more intensive use of management rhetoric and marketing communication in general and are increasingly successful among companies that are becoming increasingly aware of the real shortcomings of traditional cost calculations.

From the perspective of my dissertation, the essence of process costing is not its presumed or actual break with the functional approach but the fact that this school of thought was the one that disseminated the concepts of cost management and process management in the German literature, and that it was through it that the concept of 'resource management' *could have* acquired an interpretation throughout the German-speaking world. Yet that did not happen: the terms 'ending in management' appeared in the German language as catchphrases without well-defined content and were taken to refer to all techniques opposed to traditional management accounting.

As a result of all that, the German history of theory and current practices fail to provide a direct basis for interpreting the term *resource management*. They do, however, furnish indirect assistance through an analysis of the characteristics of decision-oriented management accounting. I believe that those characteristics – *proactive utility, orientation towards the future* – must form a part of a genuine interpretation of resource management. The word 'management', which has connotations of leadership, control, organization and improvement, is proactive and future-oriented (Wren [1994] p.3, Kreitner-Kinicki-Buelens [2004] p.12). Accordingly, resource management may involve the proactive and future-oriented regulation, organization, allocation, improvement etc. of resources. And as proactivity and future-orientation are also features of decision-oriented management accounting, the two threads join up: resource management is a part of decision-oriented management accounting.

On the other hand, it is a valid question whether resource management should only occur after a situation requiring a decision has arisen that requires quantitative data to support the decision. IN other words: is resource management necessarily a quantitative tool for supporting decision? I do not believe so. The application of resource management is not dependent on the existence of a corporate problem requiring a quantitative decision. The proactive and future-oriented management of resources can be implemented outside a specific situation requiring a decision, in the form of thinking about the future. In such cases, resource management does not support decisions but leads to decisions itself. And it is particularly important to note that this can take place even without the addition or subtraction of any two numbers.

This limitation of the German conception becomes particularly obvious if we interpret the process of management in accordance with the decision-theoretical approach established by Herbert Simon, as a sequence of decisions, a permanent problem-solving activity (Simon [1977] pp.39-81). The German logic can be integrated into Simon's model as follows: in order to allow resource management to perform its primary function, i.e. the mapping, and, to the extent possible, the quantification of resources that are relevant to a particular decision, the subject of the decision has to be known in advance, as otherwise it is not possible to establish the range of relevant resources. So resource management can come into play in the *design* and/or *choice* phases of the decision process at the earliest, but not in the phase in which the problem itself is explored (*intelligence*). Of course, that interpretation is too narrow, as simply thinking about the future – the exploration of opportunities and the intention to be proactive – are clearly part of the *intelligence* phase, yet it is one of the most important tasks of resource management

To sum up: in the German-speaking world, the interpretation of resource management as a decision support mechanism (decision-oriented management accounting) has been traditionally strong. Under that interpretation, the term ‘resource management’ is not used as a defining term, indeed, it is not used at all. For the purposes of the present dissertation, therefore, I shall take over certain aspects of decision-oriented management accounting – proactivity, future-orientation – in the definition of resource management without adopting the view that resource management is necessarily related to the preparation for specific decisions.

2.2.3 The Anglo-Saxon school

In the English-speaking world – Great Britain, the United States, Canada, Australia, etc. – we do not need to go back so far in history in order to interpret the concept of resource management. In the English-speaking world – partly due to the differences of mentality described above – costs have not been considered as important as in Germany.

In America, for instance, until very recently the theory and practice of the enumeration of resources has been determined by the requirements of external (financial) accounting (Gaiser [1998] p.68). For example, the primary objective of *costing* has been the valuation of stocks, and it was processes that met the demands of that purpose, but which were dangerously inaccurate that were used for the purposes of management accounting as well (see e.g. Horngren et al. [2008], Drury [2007]). Cost position structures hardly existed (their articulation is still poor today), and so-called *cost-pools* were used instead, which are in effect internally heterogeneous groups of costs to which identical (natural or monetary) allocation bases were allocated arbitrarily or using common sense (Atkinson et al. [2008], Horngren et al. [2008], Drury [2007], Johnson-Kaplan [1987]). The variety of costs collected in individual cost pools and the arbitrary nature of the allocation based and cost allocation ratios restricted the utility of the entire system rather severely. The most obvious indicator of that fact was the uncomfortably high ratio and lack of manageability of overheads. Another indicator was that through the cost allocation ratios, costs of all types were divided between products, which precluded the use of the management accounting system for the purpose of supporting

decisions (Nehler [2001] pp.26-32, Horváth-Mayer [1995] p.60, Brimson [1991] pp.7-10, Rørsted [1990]).

As the internal reserves of production were increasingly exploited, and driven by increasingly heavy market competition, the quest for a methodology that would ensure greater operational transparency also got under way in America. In 1987, after several undeservedly forgotten attempts[5], H. Thomas Johnson and Robert S. Kaplan published their book entitled *Relevance Lost*, which, together with the findings of the series of case studies prepared about the John Deere Component Works, placed activity logic in the forefront of interest[6] (Johnson-Kaplan [1987]). In parallel, another group of researchers worked on applying the resource-management aspects of the 'Japanese miracle' (target costing, Kaizen, quality costing, life-cycle analyses) to American conditions[7] (see e.g. Cooper [1995]).

The new methods and recommendations met genuine corporate needs, so their dissemination was very rapid. The various novel notions and directions of research achieved integration quickly, and the leading lights of the individual schools – mostly professors teaching at reputable universities – began to publish joint works. The term 'cost management' appeared with increasing frequency in the titles and chapter headings of those books. This implies that in the Anglo-Saxon world, too, resource management originated from cost management, what's more, it developed without being defined in an exact manner (see e.g. Atkinson et al. [2008], Baker [1998] p.7, Brimson [1991] p.47). Nevertheless, the meaning of resource management was focussed on modelling, as

[5] In *Relevance Lost*, Johnson and Kaplan reviewed the development of management accounting in 20th century America and in the course of that review they described several attempts at shifting the focus of management accounting and costing to meeting internal information needs ((Nadig [2000] p.11, Innes-Mitchell [1996] p.1, Johnson-Kaplan [1987] pp.152-177).

[6] Beginning in the mid-eighties, Kaplan repeatedly emphasised that American management accounting and costing – whose toolkit had hardly developed at all after 1925 – has lost all relevance in the *new world economy*. Johnson's research into the history of science revealed that at the turn of the 19th and the 20th centuries, the costing systems in use in America could be considered sophisticated for the age, but after World War II, that science stopped in its tracks – American economic hegemony and the resulting low status of efficiency meant that there was no motivation to refine management accounting methods further. The view of the two authors expressed in Relevance Lost are disputed by many people for a variety of reasons, but the large number of publications born out of that debate is in itself proof that the issue is an important one (Nehler [2001] p.27, Jones-Dugdale [2000], Taylor [2000], Sakurai [1996] p.2, Ask-Ax [1995] pp.15-18, Loft [1995] p.29, Roslender [1995] pp.73-74).

[7] The basic concept of activity logic is described in several textbooks, 'practical guides' and critical papers. See for instance: Kaplan-Anderson [2004], Bruggeman-Moreels [2003], Horngren et al. [2008], Drury [2007], Cooper-Kaplan [2001], Friedman-Lyne [1999], Kaplan-Atkinson [1998], Innes-Mitchell

indicated by the following key phrases: ‘a set of possible actions following an ABC analysis’ (Kaplan-Atkinson [1998] p.151), ‘management phrases’ (Cooper et al. [1992] p.1), ‘economic feedback’ (Cooper-Kaplan [1991] p.1), ‘operative and strategic cost management’ (Cooper-Kaplan [2001] p.19).

In the Anglo-Saxon world, resource management is usually model and action dependent. It does not refer to an approach as much as a multiplicity of models consisting of procedures – activity-based management, target costing, *Kaizen*, quality costing, life-cycle analysis, etc.. According to the Anglo-Saxon viewpoints, resource management is only able to fulfil its resource-optimising, proactive function through those procedures and models. Resource management could not exist without those procedures and models.

The Anglo-Saxon approach is characterized by a practical-minded, ‘consultant’ mindset, which uses a variety of channels to focus on aspects (e.g. introduction of systems, acceptance, target congruence, etc.) that the academic approach does not consider to be centrally important (see e.g. Kaplan-Anderson [2004], Nair [2002], Cooper-Kaplan [2001]). The consultant mindset delivers solutions for genuine corporate problems, but on the other hand its market-oriented nature inhibits the clarification of the concept of resource management.

To sum up: the Anglo-Saxon interpretation of resource management, focussed as it is on models and actions, does not furnish significant assistance for the elaboration and interpretation of the concept. It is obvious that there is a shared intention behind those models: the wish to influence costs. However, the implicit assumption that the consumption of resources can only be influenced through models or specific actions is somewhat simplistic so it would not be expedient to adopt it.

2.2.4 The Japanese approach

If the development of German thinking is to be explained in terms of sociocultural factors, this is even more so in the case of Japan. The Japanese way of handling resources is an integral part of the Japanese way of thinking and through that, workplace

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[1996], Innes-Mitchell [1995], Koltai [1994], Cooper et al. [1992], Brimson [1991], Cooper-Kaplan

relationships that suppress the individual and which build on long-term relationships, mutual dependence, the compulsion to perform and a high level of organization. (Marosi [1997] p.111-120).

Reviewing the management techniques that are traditionally considered 'Japanese' in the western literature (e.g. target costing, Kaizen, value analysis, life-cycle analyses, quality costs, etc.), three things are clear[8]. Firstly, in Japan, cost-efficiency is considered to be just as important as efficiency, i.e. the maximization of profit, itself (Sakurai [1996] p.7). There is little *slack*, i.e. little consumption of resources that could be avoided, in Japanese companies. The not purely profit-based strategy of those companies, their high social – and lately also ecological – costs of those companies demand that the costs incurred purely in the interest of the production cycle be minimized. If that were not the case, the international competitiveness of Japanese companies would be jeopardized, which could be fatal in an export-oriented economy.

Secondly, Japanese the *technological embeddedness* of Japanese techniques is much stronger, and will probably remain much stronger than that of those invented in the West. This is related to the fact that for the Japanese, the most obvious way to curb costs and expenditure is to eliminate them before they arise, i.e. to 'design them out' of the products (Cooper [1995] p.91, Cooper [1994]). 'Designing out' is primarily an engineering task, but it is driven to a great extent by considerations of economy.

Thirdly, the Japanese techniques cover all areas of corporate operation and require complete cooperation and indeed the assumption of active role in the purposeful management of resources from all members of the organization (Lee [2000] p.400-401). For instance, the cost reduction programmes that 'mobilize the entire company' – of which Kaizen is the best-known one[9] – are related, on the one hand, to the fact that

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[1991]. For the techniques adopted from Japan, see e.g. Monden [2000], Sakurai [1996], Cooper [1995].

[8] We need to be careful when we enumerate techniques of Japanese origin. Some of the procedures widely held to be derived from Japan were described for the first time by American rather than Japanese authors. The classical, 'fourfold' model of quality costing, for instance, was introduced by Juran while value analysis goes back to W. Edwards Deming. However, in what follows I shall also consider those techniques to be of Japanese origin as well, since in actual fact they were only disseminated widely after the western world of management gained cognisance – with the mediation of Japanese authors – of the results that the Japanese achieved using these techniques (see e.g. Superville-Gupta [2001], Sakurai [1996], Wren [1994]).

[9] Recently, some American authors have begun to use the term as a synonym for CPI (*continuous process improvement*) (see e.g. Edwards [2001]). It is the original meaning of Kaizen that I have in mind here.

‘designing out’ unnecessary resources is not only a concern for development and production technology, as the changes they implement roll down the entire production and logistics process and – for example in the case of value analysis – also affect the work of sales and support divisions. So no area is immune to the discovery of opportunities to increase efficiency further (Sakurai [1996] p.7). On the other hand, the Japanese are firm believers in the notion that it is the employee groups in direct contact with the products that are the most able to increase efficiency. This conviction is so strong that in their peculiar management system based on consensus-base objectives (*Hoshin*) they actually force employees to suggest developments (Lee [2000] p.401-403).

Therefore, the techniques aimed at influencing the consumption and flow of resources originating from Japan have very strong cultural and behavioural aspects. Those aspects are equally the prerequisites and the consequences of the use of those techniques. They are prerequisites, because efficiency-increasing programmes that mobilize the entire company would be impossible were they not supported by a collective of employees that has been socialized in a manner that encodes into it a fully internalised perception of its key role in influencing costs. They are also consequences because the shared realizations (achievements) need to be implemented by the employees, as enforced by *Hoshin*.

While the endeavour to plan and reduce costs form the backbone of Japanese economic awareness, until very recently the subsequent recording of the consumption of resources has been relegated to the background. Japanese costing systems are not accurate in the German sense of the word: they use traditional cost categories, unsophisticated cost transfers and allocation bases and so they are of little use for the purposes of decision-making (Cooper [1995] p.91). This, however, fails to constitute a problem as in Japan, practically nobody wishes to make decisions based on formal calculations – most formal calculation takes place ‘outside the system’, using one of the techniques listed above.

To sum up: in Japan, costs are handled through teamwork, in a specifically future-oriented manner. There is a very strong intention to influence resources and in particular to eliminate the unnecessary consumption of resources, efficiency is continually controlled and improved, i.e. *managed*. Based on the meaning of the term ‘management’, so far it is the Japanese school that is the closes to the so far undefined

‘something’ that I wish to call resource management. Thus the interpretation that I shall choose will be very close to the Japanese one, but I shall not adopt the notion that a special corporate structure is required for implementing resource management. In my view, resource management is not necessarily culture-dependent – though some of its techniques are, and the fact that companies in Japan tend to choose such techniques can be explained by local conditions.

2.2.5 Scandinavian views

Scandinavian management doctrines are rarely in the forefront of interest of practical specialists with a liking for practical guidelines. That is no accident: over the last twenty to thirty years, the Scandinavians have developed a characteristic approach to management partly based on a critical foundation that has become a fashionable trend in scientific circles while remaining difficult to comprehend for the wider public, in particular company executives in the field. The Swedish school, which has built on elements of interpretative sociology, Habermas’ critical theory and Derrida’s deconstruction and which shows some signs of postmodernism has not developed any new techniques; instead, it either interpreted existing ones (*sensemaking*), or, by positing the independence of perception and interpretation or by retracing frames of reference to the individual, proved that the existing techniques do not make sense (Kieser [2003], Weik-Lang [2001], Alvesson-Willmott [2000], Roslender [1995]).

Dissecting the social message of the Scandinavian school goes way beyond the scope of the present dissertation – suffice it to say that despite the rather strong opinions that Nordic thinkers have about management accounting, they have come up with practically no interpretations of resource management whose level of abstraction is acceptable for people in the field. The pragmatism of the paper by Ask and Ax [1995] is an exception in this respect: they suggest that cost management – and, in a wider sense, resource management – is an area in which the economic management of companies is improved in view of the prevailing boundary conditions. ‘This includes, among other things, the development of new viewpoints, methods and concepts and the adaptation of existing and entrenched ones’ (Ask-Ax [1995] p.14, *my own translation. – D.D.*).

What does that all mean? According to this approach, resource management is primarily an *attitude*. What it refers to is not a mechanical application of techniques and methods, but a way of organizing possible procedures serving business management and filling the gaps between existing procedures using new models, and most of all the development of a cognitive framework that is adequate for the 'new boundary conditions' – in essence, the criteria of success in global, transnational competition.

According to the Scandinavian conception, resource management *does not* develop out of German-style decision-oriented management accounting. It is important to emphasize that because the accounting systems, cost position structures and internal accounting of performances of Scandinavian companies has been built on German foundations (Nehler [2001] pp.17-22). However, their interpretation of resource management is different to the German one: the requirement of supporting specific corporate decisions is absent, instead they discuss the business management of companies *in general*. This also indicates that resource management in the Scandinavian sense is an attitude rather than an 'inventory of models'.

To sum up: The Scandinavian approach looks at resource management as an attitude that can exists and can be applied independently of models and techniques and whose essence is improvement and meeting challenges. This is a holistic interpretation: it does not attempt to grasp the essence of the concept to be defined through existing procedures and does not make it context-dependent. Therefore the interpretation of resource management that I shall opt for will contain a number of elements of this approach.

	German school	Anglo-Saxon school	Japanese school	Scandinavian school
Resource management is proactive, i.e. it aims to influence costs	☑	☑	☑	☑
Resource management is future-oriented	☑	☑	☑	☑
Resource management is related to specific situations requiring decisions	☑			
Resource management is model and action-dependent		☑		
Resource management is an attitude			☑	☑
Resource management is culture-dependent			☑	
Resource management is a holistic approach				☑

Table 2: The main characteristics of resource management under various approaches

(A tick indicates that the element concerned is an important one within the given school of thought.)

2.3 Resource management: a business administration endeavour and an attitude

The interpretations of resource management described in the previous sections have a number of common traits, though they are difficult to reconcile in other respects (*Table 2*). Based on the views we have seen and selecting their appropriate components it is now possible to attempt to 'assemble' a definition of resource management that matches the objective and the approach of my dissertation. I choose the rather inelegant verb 'assemble' on purpose: I shall not attempt a synthesis as I do not think it is possible to achieve one. Due to the very nature of management sciences, their lack of exactness and their permanent dependence on attitude, no single definition could be complete, yet attempting a synthesis would imply just that[10].

With all the above provisions, in this dissertation I shall use *resource management* with the following sense:

[10] Concerning the 'nature' of management sciences mentioned here see Kieser [2003], Wren [1994] pp.385-392, Drucker [1993] pp.508-511.

- Firstly, it is a *business administration task* consisting of certain elements of organization, direct management and control whose objective is to increase organizational efficiency, i.e. *cost flexibility* of the organization *in accordance with corporate strategy*, the *future-oriented influencing* of the quantity of required resources, the discovery of *saving opportunities* and the establishment of *optimal resource allocation* (the holistic approach);
- Secondly, an *attitude* permeating every level of the company that ensures that in all areas that they are able to survey, the members of the organization do their best to *eliminate* unnecessary consumption of resources, to *improve quality*, to *increase flexibility*, and that they *manage* the costs within their scopes of authority *as prudently as possible* (the particular approach).

Under that interpretation, resource management is proactive and future-oriented. It is *proactive* inasmuch as it considers the consumption of resources as a necessary but controllable evil caused by the company's operation itself, and not an inescapable 'higher power'. Resource management aims at shaping the internal and external circumstances of the company so as to obtain maximum improvement of performance for a minimal increase of costs and expenditure. According to resource management, costs can be prevented, regulated, but at least decreased or optimised. Resource management is *future-oriented* because it always understands improvement of performance as a function of corporate strategy and adapts its approach and priorities to the type and priorities of the strategy. It is 'prospective', as it continually questions the resource consumption patterns of the past and the present and seeks to allocate resources in a manner that is justified by the strategy and that also generates the greatest value. The term *future-oriented* could be replaced by the phrase *strategy-driven*.

Resource management is an approach that is *holistic and particular at the same time*, as it is based on the coexistence and interplay of two different attitudes. The holistic attitude – the viewpoint adopted by the persons with a grasp of company management and in the wider sense, the operation of the company as a whole – endeavours to identify opportunities and to make decisions on their basis while it also motivates operative staff to implement those decisions. The particular attitude – which is adopted by those whose knowledge only covers a part of the company's operations – is the viewpoint of

employees (and possibly lower management levels), and as such it is more closely tied to prevailing specific actions and processes: operations.

I believe that as a result of the coexistence of the holistic and particular viewpoints, resource management shares some *TQM-like features*. This is based on the consideration that all three sides of the 'magic triangle' of corporate operation – the cost-quality-time triangle – boil down to the same thing in the final analysis, namely the efficiency of resources. In the end, exceptionable quality, slowness and wastefulness during production all result in *unjustified* additional costs for the company, and as one of the prime objectives of resource management is the elimination of unjustified additional costs, 'resource managers' must be equally heedful of all three dimensions.

Under the interpretation I have chosen, resource management is not *model and action-dependent*. It does not come into existence because the company develops or purchases models and procedures to standardize a range of problems (in order to 'reduce complexity'), opting to view that range of problems through the omniscient model from that time onwards. It is obvious that resource management – in particular the diagnostic-type holistic variety – needs analytical and diagnostic tools, but they are worthless in themselves, without the appropriate attitude. Accordingly, diagnostic tools and formalized processes form only a thin slice of the entire toolkit, and in the ideal case, the models selected should be tailored to the prevailing corporate conditions.

Almost equally important is the fact that the existence of resource management itself is *not culture-dependent*, only its specific forms of expression are. More formal cultures engender more formalized resource-management efforts, while cultures that lay the emphasis on informal values perform resource management in a more informal manner as well. In any particular company, the holistic attitude may dominate while the particular one may be rudimentary. However, the holistic attitude is always immanently present, as – unless we subscribe to some radical version of client-agent theory – it is in the overriding interest of business administration to influence the cost level of the company, as, through its determining effect on profit levels, the survival of not only the company but also its executives depends on it. Of course, the resource-management tools used can be sophisticated or simple, depending on the dominant management attitude and the prevailing cultural context.

3. Pharmaceuticals, pharma industry

3.1 Fundamental concepts

3.1.1 Concept of medicines and the drug effect

The concept of *medicine* may obviously be defined using a definition from pharmacology or one of its legislative interpretations. Pharmacological definitions tend to be concise while those in legislation are lengthier, in line with the need to delimit legislative intent:

- 'Medicinal product: (a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or (b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.' (Directive 2004/27/EC, definitions).
- 'Medicine: any substance or mixture thereof produced for treating or preventing disease in human beings, or materials and mixtures thereof which may be used in human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.' (Act No. XCV of 2005 about medicines for use in human beings and the amendment of other acts regulating the pharmaceutical market, Article 1).
- 'By medicine we mean any material or combination of materials that, in a particular form, has properties that treat or prevent diseases in human beings or animals and which are administered to human beings or animals in order to obtain a medical diagnosis or to restore, correct or adjust organic function' (French Healthcare Code, Article L.500, http://www.leem.org [11], *translation by the author – D.D.*).

[11] The exact address: http://www.leem.org/medicament/le-medicament-definition-376.htm. Accessed: 10 January 2009.

The concept of medicine is related to the concept of therapy, which may be aimed at prevention, alleviation or control (symptomatic therapy) or restoration (fundamental therapy). Medicines form only a subset of medical (treatment and prevention) technologies alongside medical treatments, medical devices, alternative therapies etc. (see e.g. Gulácsi [2005], Vincze-Kaló-Bodrogi [2001]). They are characterized by usually being administered in a non-interventional way and modifying biochemical processes at the molecular level (see e.g. Neal [2000]).

The *pathway of medicines* in the body may be outlined as follows: the medicine may be administered using the enteral pathway (through the digestive system: orally in solid or liquid form or as an anal suppository) or the parenteral pathway (bypassing the digestive system: as an aerosol, using various injections, plasters or gels). After administration they are absorbed into the bloodstream and are distributed partly freely in blood plasma and partly bonded to plasma proteins, until they reach their 'destination'. At the destination, i.e. the primary receptor, which is a protein in practically all cases, the medicine takes effect and then either independently or as part of a medicine-ligand complex it migrates to the place where it is metabolised (undergoes biotransformation), which is usually the liver. The metabolites produced in the liver are then excreted. Excretion usually takes place in the kidneys, though in some cases medicines are excreted through bile or through the lungs, via respiration (Vizi [2002], McGuire [2000], Neal [2000], Gachályi [1992]).

At the destination site, the medicine may work its *effect* in a number of different ways and the destination site may vary as well. Some medicines (for instance local anaesthetics and certain diuretics) work through their general physical and chemical properties while others influence the body's metabolic processes (the operation of carrier molecules, long-distance carriage or the operation of enzymes). However, most medicines influence regulatory mechanisms, i.e. through 'disturbing' the carriage of stimulus either hormonally or synaptically.

There are very few medicines that only affect the primary receptor that is required for having the desired effect. The majority of medicines affect several receptors at the same time, towards which it exhibits varying affinity and has varying intrinsic efficacy in

relation to them. The unwanted effects of drug particles exerted at receptors other than the primary one are called side-effects. The strength of side-effects is a function of the affinity and intrinsic efficacy of the molecule towards various receptors[12].

The fact that medicines are aimed at remedying pathological conditions it follows that medicines administered to a healthy organism or to a diseased one, but in the wrong dose may have harmful, pathological effects. There are several example of this, including the use of performance-enhancing drugs for sports, the use of anabolic steroids for body-building, drug abuse and drug addiction all belong in this category.

3.1.2 Manufacture of medicines and the pharmaceutical industry

The process of the *industrial* production of medicines is called *pharmaceutical manufacturing*. The extemporaneous preparation of medicines at pharmacies and hospitals (the so-called magistral preparations) are usually not considered to be part of pharmaceutical manufacturing.

The *pharmaceutical industry* is the totality of companies that produce the active ingredients of medicines, excipients and formulated medicines. The pharmaceutical industry – unlike the *pharmaceutical market* – does not include the wholesale or retail trade and the hospital consumption of medicines, but a review of the interplay between those three areas must be included in any analysis of the industry. It is also difficult to draw the line between the pharmaceutical industry and other industries such as the fine chemical industry, the production of agrochemicals, the production of diet supplements, the cosmetics industry, perfume manufacturing, perfume manufacturing and, most of all, the biotechnological industry (Tőke-Szeghy [1993]). The difficulty consists in a feature of organic chemistry I have mentioned before: very similar molecules may be put to very different uses. The large pharmaceutical companies do not only use their compound libraries developed over a course of several decades for drug development, but also for the production of other preparations. Many multinationals have been active in the pharmaceutical industry and in other industries as well for several decades.

[12] For the effective mechanisms of medicines, see e.g. Vizi [2002], McGuire [2000], Neal [2000], Merck Sharp & Dohme [1994], Gachályi [1992], Knoll [1970].

There are many pharmaceutical ventures that produce active ingredients or intermediaries as the *suppliers* of large pharmaceutical corporations. There are two main types of suppliers: one is the contract manufacturer of an active ingredient developed by the client pharmaceutical company, the other sells intermediaries that it develops itself to one or more pharmaceutical firms. These intermediaries do not necessarily have a therapeutic effect, though they may have therapeutic value (Scott [2003]).

The firms in the first group are purely 'contract manufacturers': they are largely in the fine chemical industry only involved with a single – relatively low expenditure – segment of the development, registration, production and sales process of medicines, namely production, and only conduct development activities for developing production technologies at the most. The great majority of the firms in the second group are pharmaceutical companies which, in addition to the initial synthesis of the active ingredient, often conduct preclinical trials themselves as well, but they are not prepared to support the clinical and marketing expenditure of developing an active ingredient into a complete (marketable) product. It is important that with the API manufacturers in the second group, it is not the capability to formulate medicines that is lacking, but rather the tasks associated with the testing, registration and introduction of a new medicinal product are beyond their abilities.

The personal and material conditions of pharmaceutical development are regulated by the international guidelines known as Good Laboratory Practice (GLP) and Good Clinical Practice (GCP/ICH) while the similar conditions of pharmaceutical manufacturing are regulated by Good Manufacturing Practice (GMP)[13]. The GMP may prescribe special personal or material requirements for the manufacture of specific types of drugs. They include sterile drugs, medicines of biological origin, medicines prepared from plants or creams, aerosols, etc. The manufacture of those types of medicines is subject to special rules in addition to the general GMP guidelines.

[13] The corresponding items of legislation in Hungary are as follows:

- GLP: Joint Decree no. 9/2001. (III. 30.) of the Ministry of Healthcare and the Ministry of Agriculture and Rural Development on the application and supervision of good laboratory practice;
- GCP: Decree no. 35/2005. (VIII. 26.) of the Ministry of Healthcare about the clinical trials of preparations for human consumption and the application of good clinical practice;
- GMP: Decree no. 44/2005. (X. 19.) of the Ministry of Healthcare about the personal and material conditions of the manufacturing of medicines for human consumption.

3.2 Pharmacological and pharmacotechnological criteria for classifying medicines

In the present section I shall enumerate the pharmacological and pharmacotechnological criteria on whose basis medicines may be classified. An overview is presented in *Figure 4*:

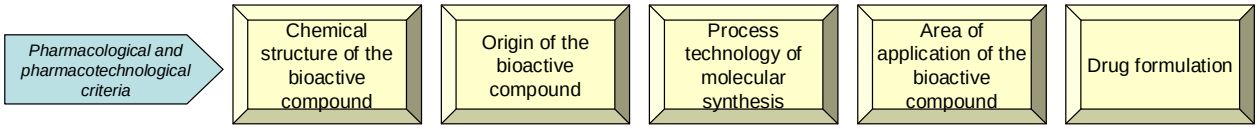


Figure 4: Pharmacological and pharmacotechnological classification criteria

3.2.1 Chemical structure of the bioactive compound[14]

A number of physical and chemical properties (spatial configuration, functional groups, electron configuration, energetic and charge conditions, etc.) determine in conjunction whether a molecule is able to exert a biochemical effect in living organisms. Molecules with very similar chemical structures may elicit very different biochemical responses. It is possible for one closely related compound to be bioactive while the other is not; indeed, one of them may be toxic while the other is therapeutic.

3.2.2 Origin of the bioactive compound

At the dawn of pharmacology, substances of therapeutic value were isolated from coal-tar derivatives originally used as dyes or – with the advent of analytical chemistry – living organism: the initial products of today's large pharmaceutical companies were practically all active ingredients available in nature (*biogeneous* substances) (Knoll [1970]). Bacteria, fungi, plant and animal organisms contain many substances of therapeutic value (quinine, opium, digitalis, penicillin etc.). Those materials are highly varied, they include some narcotics, antifebrile, antiparasitic and anaesthetic substances as well.

[14] Also known as 'active ingredient' or API (*active pharmaceutical ingredient)*, an abbreviation that appears frequently in the international – and not only English – literature.

However, as only a finite number of biogeneous medicines are available, attempts were soon underway to create *semi-synthetic* products: ‘ (…) after serendipitous biological findings had been made, certain prototypic structures were further derivatized in order to obtain compounds with improved or altogether novel effects’ (Drews [2000] p.1961). After the advent of Ehrlich’s receptor theory (the ‘lock-key’ theory) the semi-synthetic products were followed by entirely *synthetic* medicines that do not occur in nature (Vizi [2002]). Today, they form by far the largest group of medicines in the market: the technologies of organic chemistry are used to produce them in a fashion analogous to the active ingredients available in nature (Malik [2008], Drews [2000], Knoll [1970] pp.89-103). A great variety of processes are known for the production of semi-synthetic and synthetic compounds. The latest stage in development is signalled by the appearance of so-called biotechnological[15] products whose active ingredients are produced through the splicing and recombination of human, animal or indeed synthetic proteins (see e.g. Sloan-Hsieh [2007]).

3.2.3 Process technology of molecular synthesis

In theory, it is still perfectly possible today to create compounds with therapeutic value using the traditional *trial-and-error* method, but that means every compound has to be synthesized separately. This, in addition to being highly time-consuming, is also very risky (Thomke-Kuemmerle [2002]). *Combinatorial chemistry*, which underwent rapid development in the 1990’s, allows for the parallel or cut-and-paste synthesis of high numbers of organic compounds (the building and targeted screening of compound libraries), resulting in the creation of compound at an incomparably faster rate (Furka [2000], Bhalay [1999]). *Biotechnology* began to gain the foreground in the last decade of the 20th century. From the medical perspective, the discoveries concerning the human genome and protonome are the most important. *Biotechnological products* (or, alternatively, *biological therapies*) have opened up new therapeutic possibilities and introduced a new stage of pharmaceutical manufacturing (Everts [2008], Gassmann et al. [2008], Mittra-Williams [2007], Jarvis [2006], Sweeny [2002], Etkin [2000]).

[15] On the one hand, *biotechnology* is the science of isolating, replicating and splicing human nucleic acid in order to create recombinant nucleic acids, to modify genes and to transfer DNA (*genomics*). On the other hand, *proteomics* is also a field within biotechnology: it is the study of gene expression and the

3.2.4 Area of application of the bioactive compound

Some active ingredients have therapeutic value with a single diagnosis while others prove successful for a number of different diagnoses. With the increasing number of medicines it has become important to have a classification system for medicines based on therapeutic value.

The World Health Organization of the United Nations established the so-called ATC (Anatomical Therapeutic Chemical) classification system[16] in 1976, which allocates medicines

- to 14 main groups at the first level (A-D, G, H, J, L-N, P-S, V), so for instance 'C' indicates the cardiovascular system,
- at the second level, it defines therapeutic main groups indicated by a two-digit number (e.g. 'C09' refers to the main group of medicines that influence the renine-angiotenzine system),
- at the third level, it specifies the therapeutic/pharmacological group (e.g. 'C09A', the therapeutic group of so-called ACE-inhibitors),
- the fourth level of the code indicates the chemical subgroup – the actual medicine class (e.g. 'C09AA' refers to ACE-inhibitors without combination),
- finally, the fifth level indicates the active ingredient or ingredients (e.g. 'C09AA02' is enalapril).

The ATC system is a compromise between classifications based purely on therapeutic value and those also taking chemical structure into account: today it is generally used to indicate the areas of application of various drugs. By default, medicines must be licensed for each diagnosis, i.e. they may only be prescribed for indications for which the manufacturer has submitted a licence application. In exceptional cases, there are opportunities for doctors to prescribed medicines for patients for diagnoses other than those they were licensed for. This is called *off-label* use (see e.g. Decree no. 52/2005. of the Ministry of Healthcare, Hungary).

3.2.5 Drug formulation

The form in which the formulated medicine reaches the patient is called the drug formulation (or Galenic formulation). The main forms have been tablets, film tablets, capsules, syrups, powders and suppositories or – of the parenteral formulations –

sequences of proteins coded for by genes, the mapping of the tissue behaviour of proteins and the identification, analysis, characterization and modification of proteins (Sweeny [2002]).

[16] See the website of the WHO Collaborating Centre: http://www.whocc.no/atcddd/atcsystem.html. Accessed: 7 April 2011.

aerosols, plasters and ointments (gels) as well as subcutaneous implants (Knoll [1970] pp.42-44).

The method of administration is primarily dependent on the invasive and eliminatory properties of the active compound. Some medicines are available in several formulations – when various levels of effect are desired, for instance – e.g. tablet or injection or ointment or tablet, but with other drugs, there is no choice in this sense. It is the behaviour of a medicine within the organism – its pharmacokinetic properties, potential curve and therapeutic profile that determine whether it is available in multiple formulations. Of those, the most important properties are the speed, means and proportion of absorption and elimination (Knoll [1970] pp.42-44).

Research is conducted continuously to develop formulations that are maximally comfortable and safe for patients while they are also as cheap as possible (Vogelson [2001a]). According to some claims, by 2025, the classic tablet will be in a minority against formulations providing longer-lasting effects and higher adherence[17] (Signorino [2001]). Changing the format of a drug is also a customary device used to extend patent protection (se below and Salvage [2002]).

3.3 Market and business criteria for classifying medicines

In the present section I shall enumerate the market and business criteria on whose basis medicines may be classified. An overview is presented in *Figure 5:*

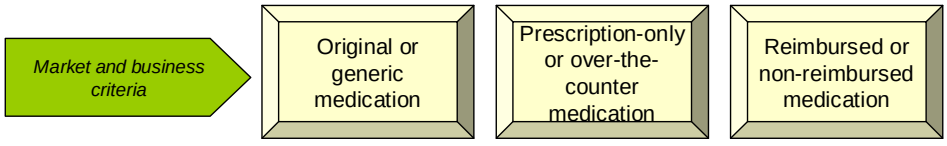


Figure 5: Market and business classification criteria

[17] Adherence: consumption of the medicine at the frequency, in the quantities and using the method prescribed by the doctor.

3.3.1 Original or generic medication

Perhaps the most important classification criteria applicable to medicines is whether they enter the market as a result of original research, or whether after patent protection of the *original* product expired, it is marketed as a copy, a *generic* product. Original development aimed at the development of a new bioactive compound (formulated medicine) costs a tremendous amount of money and takes ten to fourteen years. After it is registered, the new medicine enjoys patent protection for a certain period so as to allow the investment into its development to be recovered through a supply monopoly. However, after the patent expires, the product can be copied freely, which promotes product competition and results in a drop in prices. As a result, the market behaviour of original and generic manufacturers is fundamentally different, their products have entirely different life-cycles and cost profiles (see e.g. Kanavos-CostaFont-Seeley [2008], Gulácsi et al. [2005], Mossalios et al. [2004]).

Original products are frequently referred to as *innovative* preparations. Therefore in theory, the term 'innovative medication' is a synonym for 'original medication', but the terms are used in a somewhat misleading fashion. The reason for that is in any given therapeutic area, the newly marketed original preparations (i.e. those containing a new active ingredient) in fact have new active molecules that are very similar and differ only in the position of a few atoms or the 'peripheries' connected to their core structure. In general, there is genuine innovation behind only one or two of those, while the remaining compounds are somewhat modified versions of the 'pioneering' drug, they are me-too medications ((Lamattina [2009] pp.13-22, Sloan-Hsieh [2007] p.9, DiMasi-Paquette [2004]). So in a stricter sense, only the pioneering medicine resulting from true innovation within a particular class of drugs should be termed innovative.

It is important to point out that there is an increasing number of biotechnological products whose patents are close to expiry. This leads to a continuous intensification of the market presence of the generic substitutes of these products. Such generics are commonly referred to as '*biosimilars*' (EuropaBio [2005]).

3.3.2 Prescription-only or over-the-counter medication

Medicines can also be divided into two large groups according to whether a doctor's prescription is required for their consumption or not. Patients can only receive *prescription-only* (RX) drugs by having them prescribed by their doctors, while *over-the-counter* (OTC) medicines can be bought freely (see e.g. Mossalios et al. [2004]).

OTC drugs can have two types of history: they may be previously prescription-only originals or generics that have been shifted to the OTC category, or they may be preparations originally produced for the OTC market (Gassmann et. al [2008] p.21).

The range of medicines originally introduced to the OTC-market is rather clear: these are 'light' preparations without any disturbing side-effects that do not require medical skills and which are suitable for everyday use and self-medication. They are generally recommended against coughs and colds and also include mild pain-killers, laxatives, antidiarrhoeals, antiallergics, nicotine tablets and dermatological products. The range of drugs switched from the RX category is not much more varied, as in order for a previously RX medicine to be switched to the OTC category, a number of criteria need to be met: the medicine has to be for a disease that is basically benign, it must not have any significant side-effects, its toxic dose has to be much higher than its effective dose (also called a high therapeutic index) and it must not lead to complications if taken in conjunction with other drugs, i.e. it must not have cross-potential (see e.g. Gassmann et al. [2008], Decree No. 52/2005. of the Hungarian Ministry of Healthcare). Before a previously RX drug can become and OTC one, it has to be in the market for an extended period of time. OTC drugs may be subscribed by doctors, but they are never reimbursed by social insurance.

3.3.3 Reimbursed or non-reimbursed medication

Although pharmaceutical reimbursement programmes of various countries differ, it is generally the case that the prices of certain drugs are wholly or partly reimbursed by the social insurance system for reasons related to social considerations, public health, therapeutic interest or fairness; those are the publicly financed preparations whose admission to the social insurance system is usually initiated by the distributor. Other medicines are not on the list of reimbursed drugs; the reason for that may be that the distributor has not applied for acceptance, or that in the view of the financer they are not indispensable from the medical point of view (e.g. cold remedies), or they do not constitute a cost-efficient and successful therapy. The financer may use various reimbursement techniques in order to curb cost inflation, but they all share the general characteristic of adjusting the rate of reimbursement to a low-price, proven, bioequivalent preparation[18].

With the exception of companies specializing in OTC products – and a few 'lifestyle medicines' – manufacturers usually have a great deal of interest vested in having their

[18] Medicine reimbursement has become a specialist area in its own right. See e.g. Gulácsi [2005], Mossalios et al. [2004].

products accepted to the list of reimbursed medicines, as it is reimbursement that makes those drugs affordable for patients.

3.3.4 Interconnections between certain market and business criteria

The classification criteria listed above are not entirely independent of each other. Some of the dimensions that are theoretically independent overlap in practice. In general, the following hold true:

- If a product is OTC, there is no prescription that could be used as a basis for settlement with the social insurance system and hence by definition it cannot be reimbursed.
- The great majority of original products are RX. Very few drugs are developed directly for the OTC market, with the exception, of course, of the dietary supplements and remedies that are intended for the OTC market to start with.
- Some RX products are reimbursed, but there are many drugs in whose case the need for a prescription is not dictated by reimbursement but by the need to attend a medical specialist.

3.4 Strategy models in the pharmaceutical industry

Some of the classification criteria listed in the previous sections are such that the manufacturers make strategic decisions concerning them on the basis of a consideration of technological and market factors. I call those *strategic decision variables*, which give rise to various *strategy models*. A large proportion of the criteria, on the other hand, are the result of earlier strategic decisions (those criteria are *dependent variables*), or the set of possible decisions is constrained by higher strategic objectives (they are the *decision variables subordinated to strategy*).

The ‘original/generic’ and the ‘subscription only/over-the-counter’ criteria clearly lead to different strategy models (see e.g. Czakó [2000], Gassmann et al. [2008], Gulácsi [2005], Mossialios et al. [2004]). Therefore those are *strategic decision variables*, and I shall describe them in greater detail below.

3.4.1 Strategic decision variable: original or generic product

The distinction between original and generic products is perhaps the most important one for characterizing the pharmaceutical industry.

As I already mentioned in Section 3.3.1, *original* medicines are drugs that are marketed pursuant to original development by pharmaceutical companies and which contain a previously unknown, new active ingredient (*new chemical entity* – NCE). The time to market of original products is generally twelve to fifteen years and their development costs may exceed one billion dollars (see e.g. DiMasi-Grabowski [2007]). Those costs can only be recovered if the product enjoys patent protection for a period of time (Denicolò [2007]). During the term of patent protection – usually twenty years from announcement – the new molecule may only be used in pharmaceutical products by its inventor (see e.g. EFPIA [2008]).

Manufacturers usually apply for and receive patent protection for 'active ingredient *and* the usual excipients' (Boruzs [1999]). It is expedient to apply for the patent in the early phase of research – as soon as a potentially bioactive new compound is identified – otherwise it may be patented first by a competitor[19]. Of the twenty years of patent protection, ten to fourteen years expire while the drug is being developed, tested and licensed – provided the NCE actually has a medical application. This means that by the time the product is introduced, only about half the patent protection period remains – and the drug needs to recover the cost of development in that time. As a product usually needs eighteen months to two years to get a foothold in the market, of the twenty years of patent protection, a total of four to eight years can be truly profitable.

Once the patent expires, anyone can manufacture and utilise the active ingredient, i.e. anyone can copy the original product[20]. The copies of original products are called *generics*, or, less frequently, 'medicines available from multiple sources' (*multisource*

[19] In parallel with the product patent, the technological process of producing the compound can also be patented, using a so-called process patent. See the next footnote as well!
[20] Expiry of the product patent does not imply expiry of the process patents associated with the product as well. Generic manufacturers may only use a process to produce their copies of original products that the original inventor had not patented.

drugs, Kirking et al. [2001], Boruzs [1999])[21]. The most important feature of generics is their *essential similarity* to the original drug in the market: the generics 'are preparations of identical quality and quantity as regards their active ingredient, and of an identical formulation, which, if required, are submitted to appropriate bioavailability trials' (Boruzs [1999]).

The market entry of generics is subject to various regulations around the world. In the United States, the manufacturing and marketing of generics is rendered easier by the requirement that with the exception of specialized know-how, original manufacturers are to publish the quantitative and qualitative composition of the new drug five years after submitting the patent and no later than licensing the drug. The 1982 Orphan Drug Act eliminated the provision requiring original and generic manufacturers to submit identical documentation for the registration of their drugs. Subsequent to the ruling in the 1984 *Roche Products Inc. vs Bolar Pharmaceutical Co.* lawsuit, which was unfavourable for the company Bolar, generic manufacturers lobbied successfully and obtained permission to perform registration-related trials with their own products before the patent on the original expires (*Bolar Amendment*). The so-called Hatch-Waxman Act of 1984 allowed generics to be registered on the basis of bioequivalence: if there is substantial proof that the generic is biologically equivalent to the original, preclinical and clinical trials do not need to be repeated[22] (Tancer&Mosseri-Marlio [2002], Mossinghoff [1999]).

The legislation of the European Union does not have any elements similar to the *Bolar Amendment* (Gopal [2000]). On the other hand, the interests of original manufacturers are protected in Europe, too, by the so-called *supplementary protection certificate* (SPC), which extends the period of patent protection by the years lost in the registration procedure (Buzásné [2004], Csutorás [2004]). The SPC extends patent protection for a period of fifteen years from the issue of the first marketing approval, but only up to a maximum of five years from the expiry of the basic (product or process) patent (see Decree 1768/92/EEC).

The associated legal institution is so-called *data exclusivity* based on Article 39, Section 3 of the TRIPS Agreement, which means that the registering authority may not use the data in the registration documentation of the original product when assessing applications for the registration of generic products. Under data exclusivity, in Europe, starting from the date of the first marketing approval, original products 'shall benefit from an eight-year period of data protection and a ten-year period of marketing protection, in which connection the latter period shall be extended to a maximum of 11 years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring

[21] The exact definition of generics is stipulated in Act No. XCV of 2005 in Hungary: "a drug whose composition, as regards both quality and quantity, as well as its formulation are identical to the reference drug, whose bioequivalence with the reference drug has been proven using bioavailability trials".
[22] This simplified registration process is called ANDA (*Abbreviated New Drug Approval*), as against the standard NDA (*New Drug Approval*) required for the registration of originals.

a significant clinical benefit in comparison with existing therapies.' (Regulation 726/2004/EC, Article 14, Section 11; Directive 2004/27/EC). The institution of data exclusivity also exists in the United States, Japan and Australia, usually for terms of 4-5 years (De Ridder [2003]). In Hungary harmonization with EU low is not quite complete in this respect: data exclusivity is for a period of 6 years under Act No. XCV of 2005 and Decree no. 52/2005 (XI. 18.) of the Ministry of Health.

Due to the lack of most development-related and registration-related costs, as well as unnecessary expenditures on failed development projects, the price of generic products is much lower than the price of original products during the term of patent protection. In general, generic products tend to cost fifteen to thirty percent of the original product, and the time necessary to take them to the market varies between 3 and 6 years (Kanavos-CostaFont-Seeley [2008] p.505). Therefore, upon expiry of the patent, the price of original products drops a great deal, particularly in the case of reimbursed drugs (Niblack [1997] p.153).

In the case of original and generic manufacturers, it is more appropriate to speak of two segments of the pharmaceutical industry and to note that the sizes, cost structures, processes and human resources of companies in the two segments should not be compared *against each other*. If a single group of companies makes both original and generic products, the lines of original and generic products are handled in separate divisions, as separate strategic business areas (West [2002]).

Further specific questions have emerged through the recent appearance of *biosimilars*, i.e. the generic substitutes to biotechnological products. The time necessary to take biosimilars onto the market is longer than in the case of generic products: the range is around 6-7 years. This is explained through the fact that biological therapies are substitutable to a limited extent only; this is a 'feature' resulting from the biological peculiarities of macromolecular structures, the specificity and vulnerability of the production process, and the immunological sensitivity (*immunogenicity*) related to these. As a consequence, bioequivalence studies are not sufficient: instead of these, clinical comparative studies are required, which are suitable for evidencing not only drug efficiency and safety but also therapeutic similarity with the original product (EGA [2008]).

3.4.2 Strategic decision variable: prescription-only or over-the-counter drugs

Over-the-counter (OTC) drugs are remedies against largely harmless, everyday, brief disorders without any significant consequences. The everyday character of 'OTC illnesses' results in the OTC pharmaceutical market being much less regulated, and resembling the market of FMCG goods[23] with moderate risk and moderate profit into the balance (Stibel-Kapoor [2002]).

The philosophy of OTC products is different, too: while prescription-only drugs build on the premise that a doctor will subscribe them, OTC products urge consumers to self-medicate. But self-medication is only possible within certain limits and it has different motivations, too. The demand for healthy lifestyles, the desire for psychological relaxation, the longing for a vitamin-enriched life and the difficulty of suffering minor inconveniences (colds, mild temperatures, constipation, dust allergy, etc.) – those and similar, largely lifestyle-related factors form the foundation for the existence of OTC markets. In other words, most OTC drugs are *lifestyle drugs* (Mitrany [2001]).

The products competing in the prescription-only and the over-the-counter markets are different, with different strategic opportunities, so it seems obvious that the decision between prescription-only and over the counter should be considered as a strategic decision. On the other hand, it does raise the question whether it is possible to integrate this criterion into the 'original *versus* generic' one to simplify the analysis.

I believe that it is. Drugs enter the OTC market in one of two ways: either they are introduced directly into that market, or drugs that have been prescription-only for a long time are switched. The opportunity to simplify is present in the latter case. The OTC drugs switched from RX drugs are original or generic drugs in a late phase of their life-cycles. Their manufacturers partly make the decision to switch to their products themselves and partly they are forced to do so by the financer when it terminates reimbursement of the drug, after which the requirement for prescriptions is only a constraint on demand for the manufacturer (Stibel-Kapoor [2002]).

[23] FMCG: *fast-moving consumer goods*.

The products originally intended for the OTC market by their manufacturers form a separate category all along. They include vitamins and multivitamins, a number of lifestyle drugs, cold remedies and other 'harmless' preparations. Those products spend their entire life-cycles in the OTC market, so they require different strategic decisions. Although they may be the result of original development or they may be generic, the distinction is negligible due to the very small number of OTC originals.

So the decision variable 'prescription-only *versus* over-the-counter' can be integrated into the 'original *versus* generic' decision variable by *considering the target market of the product when it is first introduced to be the strategic decision variable*, and we interpret switches to the OTC category as special points along the life-cycles of products that require special consideration. The strategic decision variable resulting from merging the two criteria now has three values. A drug may be:

- an original, prescription-only (ORX) medicine when it is first introduced, or
- a generic, prescription-only (GRX) medicine when it is first introduced, or
- an OTC drug when it is first introduced, in which case the original *versus* generic distinction is insignificant.

This restriction introduces some distortion as it removes the distinction between originals and generics within the OTC category as insignificant. The level of distortion is likely to be acceptable, as the entry of new original drugs is extremely rare in the OTC market. It is a further advantage of merging the two criteria that the categories thus obtained match the practice of market analyses and statistics well, as there, the original and generic segments are only interpreted within prescription-only drugs while OTC products are handled separately, in the FMCG category. The resulting strategy models are shown in *Figure 6.*

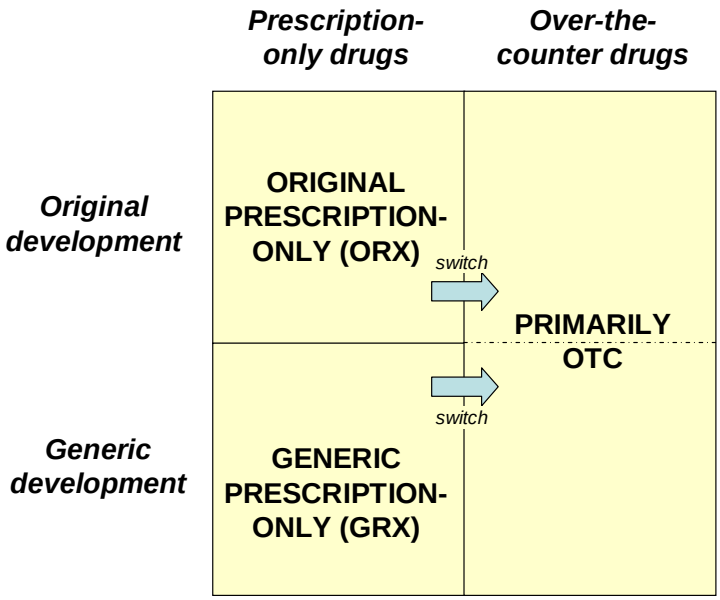


Figure 6: Strategy models in the pharmaceutical industry

We should also note that the literature contains a number of other categorisation models as well. For instance Erzsébet Czakó in her dissertation identified all four quadrants of a matrix with the above dimensions as separate strategic models (Czakó [2000]).

The strategy models of pharmaceutical companies conform to those three basic models. *Appendix 2* will add two important provisions to this.

4. Analytical model and methodology

The last two chapters have analysed the most important features of resource management and the pharmaceutical industry separately. In the present chapter, building on the previous ones, I shall establish the analytical model for the empirical study, present the research questions and hypotheses as well as the research method that I have used.

4.1 Analytical model

The analytical model for the empirical study is based on a detailed description of the process of developing, manufacturing and marketing of medicines, which, in effect, is the *value chain* of the pharmaceutical industry. The value chain is the totality of 'paths' that the products of pharmaceutical companies travel along during their life-cycles, and during which they consume various resources. It consists of a number of subprocesses and those subprocesses require different resources. The general form of the value chain is shown in *Figure 7*.

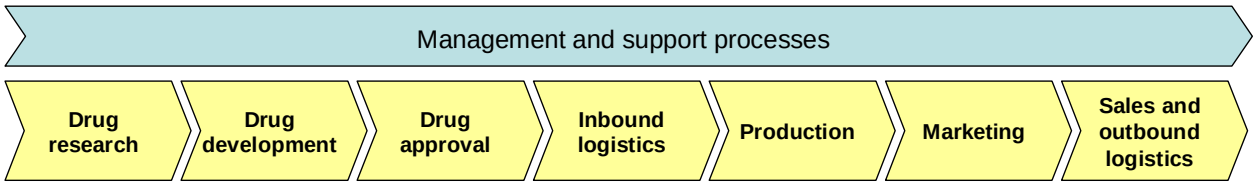


Figure 7: The general pharmaceutical industry value chain

4.1.1 Specific value chains

This generalized value chain does not take into account the significant differences between the strategy models identified in *Section 3.4*, and hence it has limited analytical utility. Instead, the general value chain needs to be differentiated so as to allocate specific value chains to each strategy model. The specific value chains need to be a great deal more detailed.

The strategy models defined in Chapter 3, which shall require separate specific value chains, were as follows:

- Original prescription-only (ORX) segment (and value chain)
- Generic prescription-only (GRX) segment (and value chain)
- OTC segment (and value chain, with respect to first market entry)

The various phases of the value chains exhibit radically different characteristics. The decisions made in the early phases may determine the scope of action in later phases, i.e. they may cause path dependence. Changing an already developed synthesis pathway, for instance, may result in disproportionate costs in production technology, regulatory and documentation costs. The ratios of controllable and uncontrollable costs and expenditures also vary (Coenenberg [2003]), along with the degree of technological determination of processes. The use of computerized molecular design methods, for instance, may represent a significant item of fixed costs, but it can reduce the costs of other capacities. The value chains also differ in the numbers of individual professions and organisational units they involve. Molecule design, for instance, is purely a pharmaceutical research task, but the later stages of clinical trials involve doctors, pharmacists, healthcare economists and marketing specialists working in cooperation.

4.1.2 Three main groups of resource management tools

Based on the above considerations, resource management can be provided using various solutions in the individual phases of the value chains. I conjecture that it is helpful to distinguish the *scientific and technological solutions* associated with basic process technologies, the *work organisation solutions* that aim to improve coordination and communication within the organisation and the so-called *business tools*, which consist of performance management and marketing techniques.

Under *scientific and technological solutions*, I include all instruments and processes that act on the fundamental processes and thereby influence the logic and the procedures of pharmaceutical research and development. They largely consist of scientific and/or engineering knowledge, or its application, and are often embodied in technological innovation. New computer processes, new methods of analytical

chemistry or the pharmaceutical application of biotechnology are all examples of scientific and technological solutions.

I understand *work organisation solutions* as referring to organisational interventions aimed at increasing efficiency through improving coordination and communication within the organisation. They include the structural and person-oriented tools of coordination documented in management theory (see e.g. Dobák [2006]). The creation of projects extending across several organisational units, the division of a process consisting of sequential stages into blocks of tasks that can be performed in parallel, or the conscious and enforced improvement of communication between the persons concerned are all examples of work organisation solutions.

Business tools are the management procedures and methodologies that aim to increase efficiency through the cycle of planning, setting objectives, subdividing objectives, cost calculation, performance measurement and performance evaluation. Process cost calculation, net present value calculation and portfolio analyses are examples. In a specifically pharmaceutical context I also include here the forward-looking planning tools such as marketing analyses and healthcare economics analyses whose objective is to estimate the future profitability, market attraction and acceptable price level of products. So the category of business tools includes the methodologies called performance management tools as well as those known as marketing tools in management science.

4.1.3 Different perceived relevance of resource management tools

We may also assume that – while, due to its multidisciplinary character, resource management is a common feature of all strategic models – the relevance of the individual resource management tools as perceived by the decision-makers who use them varies between the individual strategic models. By *perceived relevance* we mean the opinions of managers concerning the closeness of the connection between use of a particular tool and the achievement of strategic advantage. I shall consider a particular resource management tool to be relevant if, in the opinion of the managers who use it (or those supervising its use), it is of critical importance for achieving strategic competitive advantage for pharmaceutical companies.

At a high level of abstraction we can assume that in any strategy model, the perceived relevance of a resource management tool is dependent on the following factors:

- its intrinsic *potential*, i.e., more specifically the relative resource-intensity of the section of the value chain in which it is used (relative to other sections of the value chain); the extent to which it will be able to *influence* the resources (in scope or depth) consumed in the section concerned; and the *strategic advantage* that the company may gain through this;
- the practical utility of its *implementation*, i.e. the level of organizational adaptation that it requires, the methodological and IT background it needs, and the degree of support it can expect from the organization on the basis of sociocultural characteristics.

The perceived relevance of a resource-management tool for decision-makers is proportional (*ceteris paribus*) to its potential and the probability of successful implementation. All of those considerations are summarized in a model in *Figure 8*, which thereby also depicts the analytical framework for the empirical study:

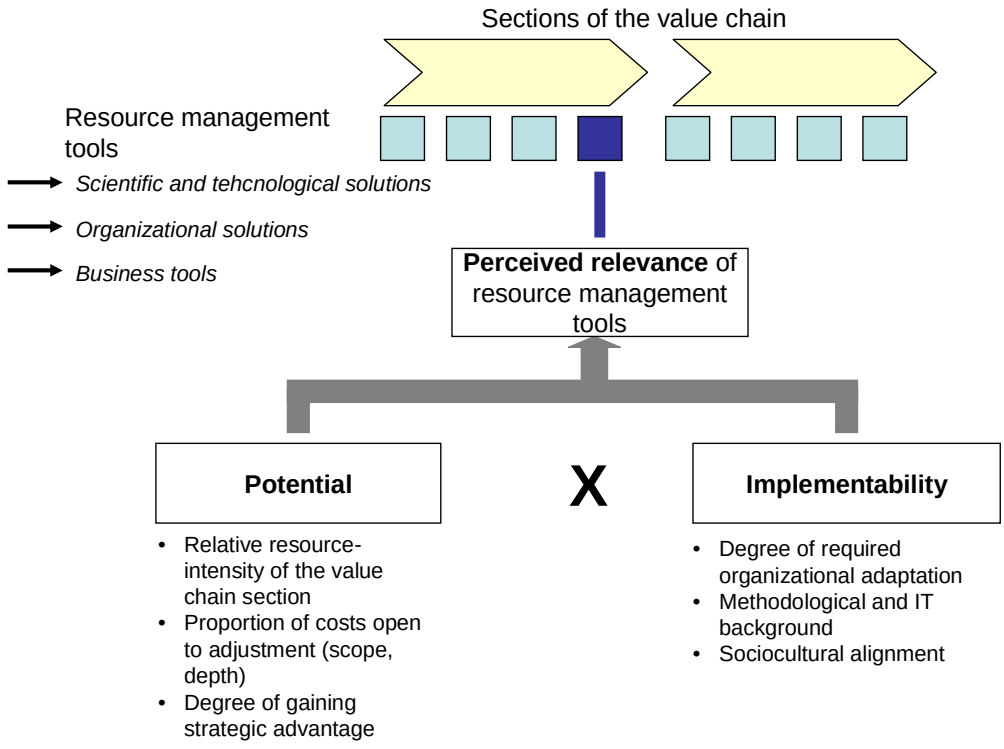


Figure 8: Analytical model for resource management in the pharmaceutical industry

During the empirical research – when it comes to the analysis of the perceived relevance of individual resource management tools – I shall at least attempt to separate potential and implementability. Deeper factors will be presented wherever the research yielded special results concerning them. In this respect, the analytical model has been simplified somewhat relative to the draft dissertation, because the majority of my interview subjects were unable to interpret the multi-level, complex analytical framework that I described initially.

4.1.4 Exclusion of the OTC strategy model

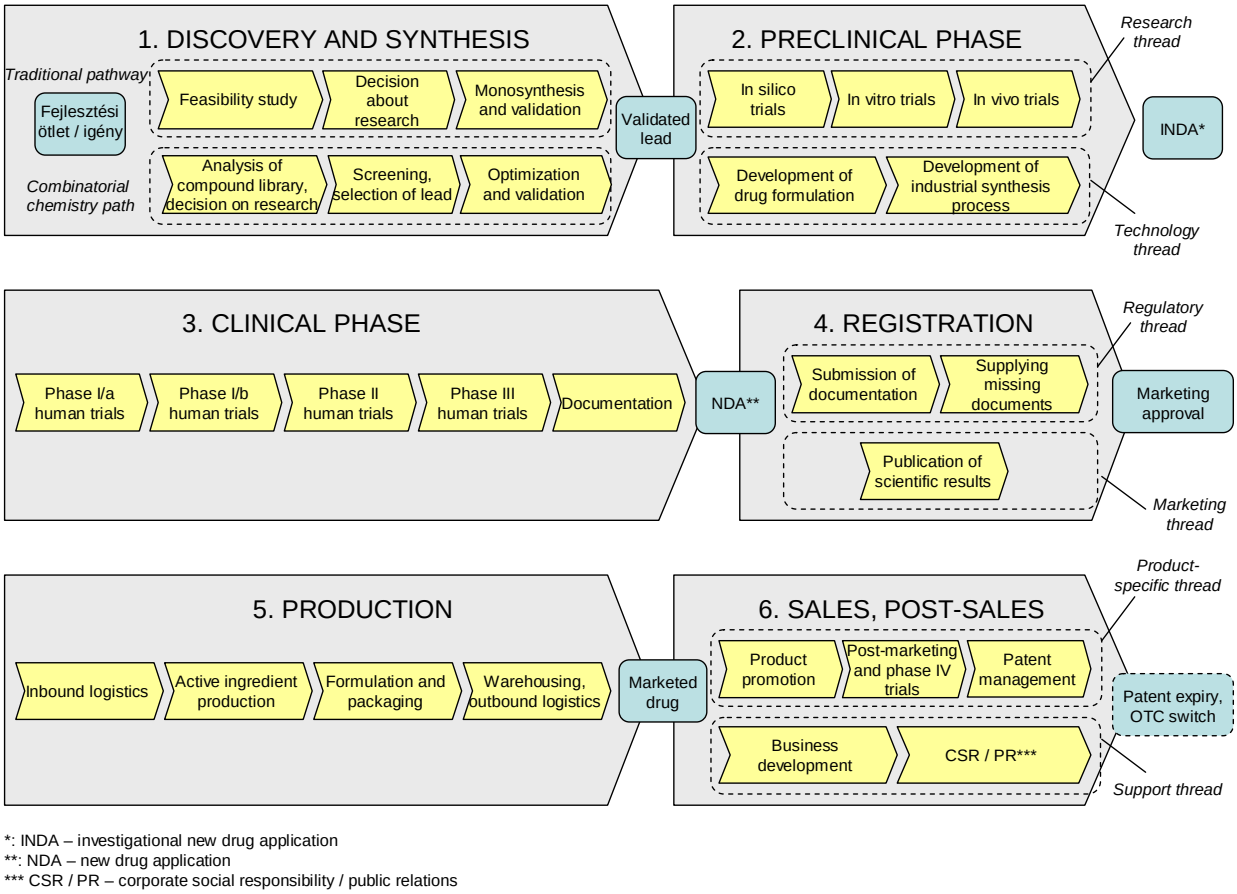
My dissertation does not cover the OTC strategic model. One of the reasons for that is based on the reviews of my draft dissertation it was clear that, due to the complexity of the subject, my research had to be structured and simplified. The other reason is the strict limitation on length, which does not allow me to include detailed reviews of all three of the business models. Eliminating the OTC model appears to be the "least painful" simplification option: that model tends to exhibit the characteristics of the market of consumer goods in general which are well-documented in the literature, so the added value of my research would have been smaller there, anyway. There exist a number of previous research papers concerning the OTC model as well, and the sample available in Hungary is also sufficient, so I certainly intend to add an analysis of that model to my study in the near future in order to fill the gap.

However, for the sake of completeness I shall also provide a description of the value chain of the OTC model as well, as it was already included in my draft dissertation.

4.2 Specific value chains of the analysed strategy models

4.2.1 Specific value chain of the original prescription-only (ORX) strategy model

The specific value chain for the original prescription-only (ORX) strategy model is shown in *Figure 9*:



*: INDA – investigational new drug application
**: NDA – new drug application
*** CSR / PR – corporate social responsibility / public relations

Figure 9: Specific value chain for the original prescription-only (ORX) strategy model

The life-cycle of a bioactive molecule begins when the development idea (demand) arises. The idea may come from the company's researchers through intuition or previous experience, but more recently, the purposeful generation of ideas has become the norm, which means that *target* proteins are sought. The decision may be made to attempt producing the compound envisaged using traditional monosynthesis. If that path is opted for, in many cases – albeit not always, and especially not always to the same depth – a feasibility study is performed. If the outlook is favourable, a systematic trial-and-error

search is launched on the basis of a scientific hypothesis to 'produce' a lead, preferably with a low molecular weight. This is a very slow and costly process, a single researcher cannot synthesize more than a hundred compounds per year (including analysis, validation and the optimisation of the molecule). It is difficult to establish the period of time required for molecular synthesis because the beginning and the end of a *discovery* are difficult to define exactly (Sweeny [2002] p.5). The costs amount to some ten to twenty percent of the total research and development budget – sources differ on this point (Gassmann et al. [2008], DiMasi et al. [2003], Sweeny [2002], Thomke-Kuemmerle [2002], Bhalay [1999]).

The method of reviewing compound libraries *created previously* using combinatorial chemistry methods to find compounds that match the development idea is a significant advance and can go ahead in parallel with the above procedure. The review is followed by the decision to initiate the development and the targeted, high-throughput screening of the compound library in the interest of selecting a lead. The leads selected through the screening are validated and optimised, then – if the results of the validation are favourable – all of their physical, biological and chemical properties are mapped and documented in detail, including the contamination that occurs as a result of the process of synthesis. Subsequently, the lead is prepared for preclinical trials (Sloan-Slieh [2007], Mullin [2003], Sweeny [2002], Thomke-Kuemmerle [2002], Furka [2000]).

Three things need to be added at this point:

- Firstly, the lead envisaged – which is effective on the target – is not necessarily a *single* compound. The notions of researchers often only outline the approximate structure of the molecule, the location and position of functional groups and the arrangement of bonds etc. A number of different compounds may have the properties sought. In most cases, the therapeutic effect is only suspected, it is too early to select a specific indication. That is why research programmes often start with a very large number of leads, whose majority proves unsuitable during the preclinical tests. On average, only one in ten molecules pass the first screening, the computerized (*in silico*) experiments (Thomke-Kuemmerle [2002]).
- Screening is usually performed on a *previously created* compound library. The creation of a new compound library for the purposes of a development project is rare – companies characteristically have libraries of several million compounds, which are the repositories of the best part of their 'tacit knowledge', and it is those libraries that they review more or less regularly, seeking development opportunities. The main methods for extending those libraries are the 're-entry' of molecules selected

through screening after optimisation and a systematic study of the flora and fauna (Sweeny [2002] p.9).

- The research concerning molecular targets – target proteins – is exceptionally important in relation to the discovery of new drugs. They are also highly resource-intensive, but they constitute one of the springboards for pharmaceutical innovation. The mapping of a new target protein takes two and a half years on average, while its costs amount to some four percent of the total cost of the associated pharmaceutical development project (Sweeny [2002] p.5).

At that point, the compound enters the second, preclinical phase of pharmaceutical development (Gachályi [1992] p.155). Preclinical trials commence by using computer models to perform toxicity, efficacy and kinetic (stability) trials. This process is called *in silico* trials, which filters out ninety percent of the compounds[24] (Sloan-Slieh [2007], Curry [2002] p.61, Thomke-Kuemmerle [2002] p.622). The next step consists of *in vitro* trials conducted in a laboratory setting on organ preparations and tissue cultures. The objective of this is to filter out molecules that are toxic or ineffectual in a human body. By the end of the *in vitro* trials, ninety-eight percent of the leads that entered them are dropped – only some two percent are suitable for *in vivo* animal trials (Thomke-Kuemmerle [2002], Gachályi [1992]). The compounds that pass the *in silico* and *in vitro* stages are usually patented prior to the commencement of animal trials.

The primary purpose of animal trials, which are the subject of ethical debate, is to establish the toxicity profile of the bioactive molecule. Although it is only possible to convert the results of animal trials to results applicable to human beings using special conversion tables, they are indispensable in order to improve the safety of clinical tests. In the course of *in vivo* trials, the acute (immediate), subchronic (over a few weeks) and chronic (longer term) toxicity of the compound is analysed and the drug's *approximate lethal dose* (ADL) is determined. The stability of the molecule is also tested and *carcinogenic* and *mutagenic* properties are also tested for along with any effect on fertility or developing embryos. The latter are called the *fertility* and *teratology* trials (Sweeny [2002] pp.4-5, Gachályi [1992] pp.156-164).

The preclinical trials regulated by GLP (*Good Laboratory Practice*) constitute the longest phase of pharmaceutical development. They may extend to five or six years and

[24] Computer software provides information about the expected toxicity and efficacy of a compound based on the data and behaviour of known compounds and physicochemical laws.

their costs represent some ten-twelve percent of the total research and development budget (EFPIA [2008], Sweeny [2002]). The most time-consuming trials are the carcinogenicity trials, as the test animals need to be monitored to the ends of their lives, which may take 18 to 30 months depending on the species of animal used (Gachályi [1992] p.164).

It is expedient to define the form of administration and the formulation of the drug for human therapy in parallel with the preclinical tests. This is required because the excipients also influence the bioavailability of the compound, and if they are only added to the active ingredient later, this my render the previous test results useless. The form of administration is usually determined by the pharmacokinetic properties of the drug, but modes that are easy to manufacture, formulate, package and store should be aimed for as far as possible. After the formulation is determined, but still in parallel with the preclinical trials, the development of the drug's manufacturing technology begins to be developed and the choice of the production site is also made in accordance with the results of the life-cycle analyses prepared by marketing (Henry [2002], Gachályi [1992] p.155). The associated costs, including the establishment of the system of quality management requirements, can reach eight to nine present of the total research and development budget (EFPIA [2008], DiMasi et al. [2003]).

Developing the production technology is not a single-step process. Until clinical trials actually prove that the drug is efficacious and would go into production, *scaling up*, i.e. developing the laboratory path of synthesis to meet the requirements of industrial production, is not worth investing in. Therefore the objective of the work in process chemistry that takes place in parallel with the preclinical trials is to establish a technology that is suitable for industrial use, but it does not necessarily have to be optimal, consistent with batch sizes and finalized. It is a further task of process chemistry to develop the analytical techniques to be used by quality control in order to establish the purity, contamination profile and target parameter compliance of the finished products (Nagy [2003]).

The last twelve to eighteen months of the preclinical phase is taken up with the finalization of the trial documentation and the design of the human trials. If the company undertaking the development finds the preclinical results promising, it will submit an application for a permit to conduct clinical trials to the drugs administration. That is the so-called INDA (*investigational new drug application*). Until a response is received, human trials are strictly prohibited (*clinical hold*, Woodcock [1997]).

About half the compounds that enter the preclinical phase reach clinical trials (see e.g. Nesbitt [2006], Robinson-Cook [2005]). In the first phase of the clinical trials, the so-called *human phase I trials*, the drug's tolerability and pharmacokinetic properties are tested (ADME – *absorption, distribution, metabolism, excretion*). Researchers attempt to determine the dose that the human organism can take without damage. First of all, they test the drug's accumulation, administering increasing doses to the participants (phase I/a, *ascending dose*), then longer-term kinetic properties are mapped (phase I/b, *multiple dose*). During that phase, the drug is administered in identical or almost constant doses at a lower frequency. If possible, the pharmacodynamic properties of the drug are also monitored (Gassmann et al. [2008], Thomke-Kuemmerle [2002], Vogelson [2001c], Gachályi [1992], Jávor [1985]).

Phase I trials are conducted using a small number (18 to 24 people) of *healthy* paid volunteer subjects allocated to the groups in a randomised fashion. A control group on placebo is uses all the way through the observation. The trials can be single blind or (more frequently) double blind tests. In the former case, it is only the subjects that do not know whether they are getting placebo or not, while in the latter case, the doctors treating them do not know, either. These trials, which may only be conducted at accredited facilities, may only use healthy male subjects – women and people with health disorders are only admitted if other subjects are not suitable for the trials for ethical or biological reasons[25]. The 'active part' of phase I (the course of drugs itself) is completed in two to three weeks, but the evaluation of results and the preparation of documentation may take 18 to 24 months (Robinson-Cook [2005], Watkins [2002], Vogelson [2001b], Gachályi [1992]).

During *human phase II trials*, the drug is tested on a medium-size group of *patients*. The objective is to test for tolerance and efficacy, including the determination of the optimal dose, the documentation of pharmacokinetic properties and the monitoring of additional medical conditions and side-effects[26]. The exact indication of the drug, i.e. the exact disease or pathologies that the drug is recommended for need also be determined in phase II at the latest. The sizes, increments and frequency of doses in this phase are defined as a function of phase I results (Robinson-Cook [2005], Gachályi [1992], Jávor [1985]).

[25] E.g. cancer drugs with a strong chemotherapeutic effect or gynaecological products, etc.

[26] Regardless of whether it is due to an additional medical condition or a side effect, an unfavourable reaction to the drug is initially considered to be an *adverse event* (AE), then, once the link between the drug and the adverse event is established, it is reclassified as an *adverse drug reaction* (ADR; see e.g. Robinson-Cook [2005]).

The structure of phase II trials is similar to that of phase I trials. They also require around two years, but they are somewhat less strictly regulated and may be performed in more locations. The participants are patients who do not need to be paid, which reduces the cost of these trials. On the other hand, costs are increased by the large number of participants and the large number of tests that need to be performed. As a result, in many cases, so-called *pilot phase II trials* are conducted with a small group of patients (9-12 people) in order to clarify whether there is any point in trying the drug on a larger group of (100-200) patients (Watkins [2002], Gachályi [1992]).

In the last phase of the clinical trials, the multi-centre *human phase III trials*, the drug is tested on large groups of patients around the world. The primary objective is to establish therapeutic efficacy for a specific group of diseases, but the indication may also be adjusted, side-effects are screened, the effects of additional medical conditions is clarified and the documentation required for registration is also prepared during this period (Robinson-Cook [2005], Gachályi [1992], Jávor [1985]).

During phase III, which may take as much as three and a half years and consumes tremendous resources, the effects of the drug are compared against those of similar drugs already in the market as well, and preparation for promoting the product also begins. In theory, phase III trials do not need to be conducted at specialized institutions, but having reputable clinics participate lends authority to the trials. Procedural consistency is a fundamental requirement. The number of participating patients almost always exceeds five hundred but can be as high as several thousand and there have been examples of trials in which the number of participants reached thirteen thousand. The subjects are divided into groups using statistical methods, and the results are also analysed in that fashion (Watkins [2002], Peck [1997]).

Each of the human phases require a separate permit. Clinical trials are regulated by GCP (*Good Clinical Practice*) (see e.g. Robinson-Cook [2005]). Since 1990, efforts have been made within the framework of the ICH (*International Conference on Harmonization*) to standardize the American, European and Japanese GCPs and to prevent multiple applications, but in most countries of the world, 'administrative protectionism' is still strong (Orbán [2003] p.83, Niblack [1997], Woodcock [1997]). At least forty percent of the costs of developing a new drug is spent during the sixty-eight months that clinical trials require on average, which means that both in absolute terms and proportionally, clinical testing is the most expensive phase of pharmaceutical development (EFPIA [2008], DiMasi et al. [2003], Sweeny [2002]).

Once the clinical trials are completed, the documentation of the drug, which may exceed a hundred thousand pages and which contains all the evidence collected and inferences drawn during the multi-centre studies, is compiled. The documentation, presented in a

strictly regulated format, is submitted to the registration authority, which makes a decision to approve or reject the application for registration on the basis of the test results, the compliance of the documentation and the validity of the statistical methods applied (Robinson-Cook [2005], Vogelson [2001c], Peck [1997] p.163, Versteegh [1997] p.155). In parallel with the registration process – provided there is no significant risk of rejection – the companies begin to disseminate the scientific results of the clinical trials to a wider audience.

In general, original manufacturers do not take the risk of having their molecules 'failed' by the drug registration authority, so they do not even try to register any compounds that performed inconsistently or unsuccessfully in the clinical phase. Some seventy to ninety percent of drugs that reach the clinical phase meet that fate; forty percent are dropped in the last one, phase III (Sweeny [2002] p.6, Thomke-Kuemmerle [2002] p.622).

Of all the phases of the development process, the length of the registration procedure shows the greatest variation: in recent years, it averaged at 18-19 months, but some drugs have been registered in 6 months while others took a hundred and fourteen months to be granted approval. The cost of registration is 45 million dollars on average, i.e. 3 to 5 percent of the total cost of development (Robinson-Cook [2005], Salvage [2002], Watkins [2002], Cool-Röller-Leleux [1999], Findlay 1999). In relation to the registration procedure, as a closing part of the clinical trials, brief bioequivalence trials may be conducted using healthy volunteers in order to show that the drug as used for the trials is completely identical to that going into production (Sweeny [2002]).

Once registration is approved, the product can be manufactured and sold. The first phase of production is inbound logistics, i.e. the procurement, delivery and storage of the materials required for production that the company does not produce itself. Due to the strict quality management requirements, pharmaceutical manufacturers usually purchase their raw materials and supplementary materials from permanent partners.

The first phase of actual production is the manufacturing of the active ingredient using the multi-step synthesis process that the technological engineers probably developed in parallel with the preclinical tests. The number of steps required to produce an active ingredient varies between 'many' and 'very many'. There are production paths

consisting of thirty to fifty steps that take several months to complete, and the complexity of the technology involved is only likely to increase as the complexity of the drug compounds themselves grows. Excipients are mixed with the active ingredient during the formulation phase, and the preparation is 'brought to its final shape' using automatic production lines. The medications coming off the production lines are then packaged and delivered to a finished product warehouse, which is often away from the production plant. Wholesalers take delivery of the goods at those warehouses.

Drugs are manufactured in so-called batches. In effect, batches are predetermined quantities of specific drugs to be manufactured at the same time. Their length is determined on the basis of technological, quality management and operational efficiency. Batches cover the entire technological process, they can only be interrupted after the active ingredient is produced, before formulation. Batches need to be documented all along – in the case of a technological process that converts five tonnes of raw materials to a few kilograms of finished product, this may easily amount to several thousand pages.

The entire manufacturing process is subject to extremely strict GMP (*Good Manufacturing Practice*) regulations that contain detailed provisions concerning suppliers, the raw materials obtained from them, their storage, transportation, manufacture, the machines used for manufacture, manufacturing facilities, batches, formulation, packaging, the storage of finished products and the responsibilities associated with all those items (in Hungary, Decree no. 44/2005 (X. 19.) of the Ministry of Health). The GMP prescribes continuous and detailed documentation and maximal operational discipline, which makes it unprofitable to introduce any small changes to the technological process. The costs associated with the GMP amount to about a quarter of all *manufacturing* costs (Rosenberg-Weiss [2002]).

Reviewing the length of the phases of development it transpires that twelve to fifteen years pass from the commencement of development until the drug enters the market (see e.g. EFPIA [2008]). When the drug begins to recover its development costs along with those of the failed molecules, about two-thirds of the patent protection period is likely to have expired already. As a result, the drug needs to be promoted as quickly as possible, and this requires active marketing work. In the original prescription-only market, marketing has a double function: on the one hand, it is product-specific and needs to show that the product is effective, needs to publicize its advantages and promote it towards the prescribing doctors while also managing existing patents. On the other hand, marketing also makes an increasing contribution to the commercial success of original pharmaceutical companies, and it merges with business development and strategic communication. In this sense, the establishment of smooth cooperation with clinical

research organizations, successful advocacy in negotiations with the financer, improving the confidence of patients in the drug and identifying any gaps in the market that could be filled with drugs are all marketing tasks as well (see e.g. Calfee [2002], Harms et al. [2002], Szabóné [1997]).

In relation to marketing work, I should also mention the clinical trials which are conducted after the drug has been introduced onto the market. The costs of such trials are often accounted for as research and development costs and amount to about 12 percent (EFPIA [2008], Nesbitt [2006]). Commercially available drugs may undergo two types of tests:

- The purpose of *human phase IV trials*, which are closer to authority supervision (pharmacovigilance) is to extend knowledge about the drug, to collect data, to explore rare co-administration effects and side-effects, to seek further indications and markets, to refine administration methods and to promote the drug (Robinson-Cook [2005], Laporte-Rawlins [1999], Woosley [1997]). Phase IV trials are conducted on volunteers, with the manufacturer providing the drug. The manufacturer also develops the test protocol and is entitled to control and influence the tests within the limits prescribed by legislation.
- The purpose of *postmarketing (non-interventional) tests*, which are more distant from pharmacovigilance, is similar, but they are more marketing-oriented. In those, the manufacturer may not influence the treatment strategy and product choice, or the compliance of the participants. Patients finance their own drugs, and the companies are primarily trying to secure the interest of the participating doctors. Postmarketing trials are only subject to a registration requirement (Robinson-Cook [2005]).

During the term of patent protection, marketing of the drug is continuously focussed on using branding and other tools to pre-empt competition from generic products. When the patent is about to expire, the role of marketing becomes even more important and legal elements are also added: original manufacturers use every patent litigation opportunity they can to extend the market monopoly of their products for a time (see e.g. Findlay [1999] pp.229-231). After the generic products do occur, marketing takes care of the remaining life-cycle of the original product, maintains contact with subscribing doctors, manages the advertising strategy and seeks possible opportunities for developing the

product further. It also has the task of liasing with the regulatory authorities and – if the possibility arises – optimising the timing of the product's switch to the OTC market (see e.g. Hollenbeak [1999], Streitné [1999]).

4.2.2 Specific value chain of the generic prescription-only (GRX) strategy model

The strategy of generic pharmaceutical manufacturers is based on 'copying' molecules that have already been developed. This strategy model misses the phase of *serendipity* that characterizes basic research in originals, on the other hand, the physico-chemical properties of the drug molecules to be reproduced are largely known thanks to the tests of the original compound. So the value chain of this strategy model is much shorter in time: the very complex development and registration phase characterizing original manufacturers is practically omitted (Findlay [1999] p.229). That simpler value chain is indicated in *Figure 10* below:

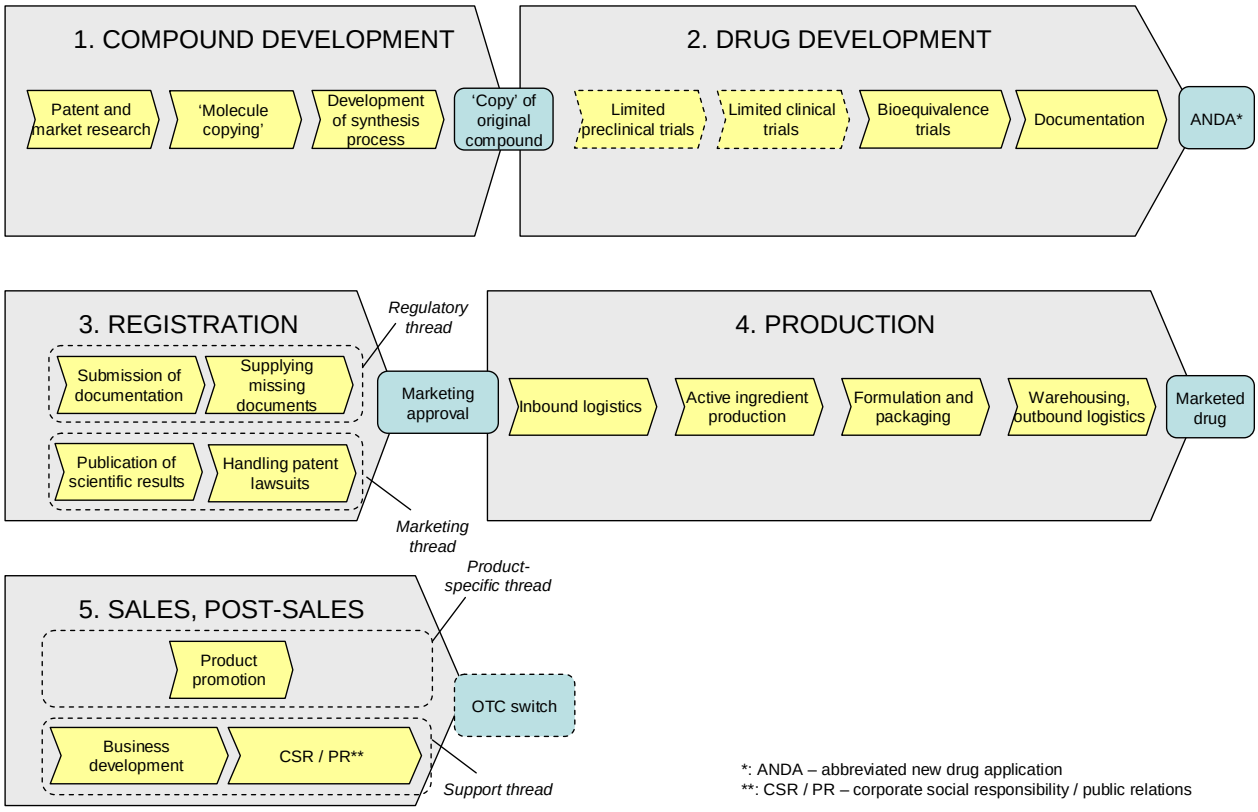


Figure 10: Specific value chain for the generic prescription-only (GRX) strategy model

Logically, the value chain of generic manufacturers also begins with a development idea, but its nature is completely different: generic companies continuously monitor the

originals whose patents are about to expire and do research into technological and other documentation about such drugs. They attempt to produce the products whose patents are about to expire using a process that the originator had not patented but which is suitable for industrial synthesis. Development of the production technology also includes the establishment of production standards and norms.

If the alternative synthesis path is successful, the research and development phase, which lasts twelve to twenty-four months, is completed. Limited preclinical and clinical trials follow. They are only required in the case of so-called supergenerics, which contain some additional value, usually a difference in the active ingredient relative to the original molecule. If the generic drug does not differ from the original or only differs in its excipients, it is sufficient to prove the bioequivalence of the drug[27] (Rouhi [2002a], Rouhi [2002b], Findlay [1999], Boruzs [1999]).

Bioequivalence tests are usually completed in 18 to 24 months. The documents certifying equivalence and compliance with manufacturing requirements are submitted to the authority that will register the drug (*abbreviated new drug application* – ANDA). Registration takes roughly the same period of time, but it may vary as a function of the number of repeated trials prescribed or additional documents requested by the authority (Mossalios et al. [2004], Findlay [1999] p.229). In most cases, the period of time required for registration depends primarily on whether the originator sues the generic company for patent infringement. If the generic manufacturer submits the registration application denying patent infringement or contesting the patent, a lawsuit is inevitable and this results in an automatic suspension of the registration procedure (see e.g. Rouhi [2002a]).

Generic manufacturers aim to have their product at retailers on the day the patent expires. In practice, they do not always succeed due to litigation and protracted preparation for manufacture (Hollis [2002], Rouhi [2002a], Hermann-Harnett [2001]). The development and market introduction of a generic drug takes three to five years on average and only costs one or two million dollars. However, due to the risk of lengthy litigation, generic manufacturers often begin to take preparatory steps seven years before the planned date of market introduction (Findlay [1999]).

Once the generic is registered, it can be sold in the market. The manufacture of generics is also subject to the norms and provisions of GMP. The procurement of raw materials, the production of active ingredients and formulated drugs, packaging and delivery are all performed identically to originals, with the exception that generic manufacturers often procure their active ingredients from suppliers – largely companies in the fine chemical industry (Decree no. 44/2005. (X. 19.) of the Hungarian Ministry of Health, Mullin [2003], McCoy [2002], Rouhi [2002b]).

In branded prescription markets, the launch of generics is preceded by intensive marketing work. The acceptance of generic products in increasing all the time, in fact they are given preferential treatment by public financers on account of their lower prices and the resultant reduction in public spending (Mossalios et al. [2004]), yet they still face a number of prejudices. Therefore the main objective of generic marketing is to show that the product is not only identical with the original in accordance with regulatory criteria, but it is actually identical in every respect, while being offered for a better price (Rouhi [2002a], West [2002]).

Once the position of the product has been established, the focus of generic marketing shifts. Its task from then onwards is to extend the life-cycle of the drug as far as possible. Unlike originals, whose profit is made during the years of patent protection, the profit on generic drugs is distributed along the product life-cycle. Naturally, a switch to the OTC market is also an option for generics.

4.3 Presentation of the research questions and hypotheses

In my dissertation I study the solutions that pharmaceutical companies use in order to improve efficiency in the original prescription only (ORX) and the generic prescription only (GRX) segments, along with their perceived relevance. I have revised the questions and hypotheses to be used as the basis of research significantly on the basis of the criticisms of my draft dissertation that rightfully objected to the trivial or construed character of some of my hypotheses. As a result, a number of the general statements

[27] In *Figure 10*, a dotted line indicates that preclinical and clinical trials are not always required.

concerning the complexity of resource management in the pharmaceutical industry and the large variety of tools in use no longer appear among the hypotheses. I now see those theses as starting points on which deeper and more specific research questions and hypotheses can be constructed.

4.3.1 The first research question: the specific tools in use

Accordingly, my *first research question* concerns the specific solutions within the three categories of resource-management tools that I designated (scientific and technological solutions, work organisation solutions, business tools) that are actually used to improve the efficiency of companies in the original and generic pharmaceutical industries. This is an exploratory research question that has no explicitly formulated hypothesis linked to it. However, I could already *conjecture* before performing the research that scientific and technological solutions would largely focus on accelerating the pharmaceutical development process and eliminating risks in good time, while work organisation solutions would be aimed at achieving more fluent cooperation between organisational units with varying attitudes and competencies and business tools would largely consist of long-term and medium-term analyses.

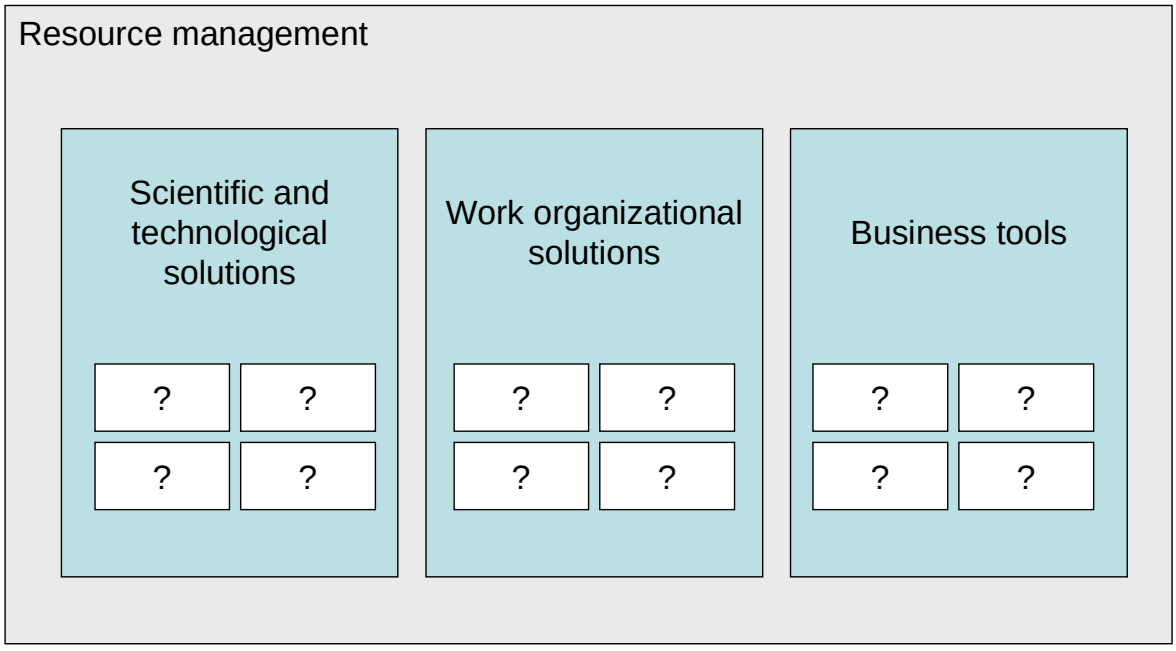


Figure 11: Resource management solutions in the pharmaceutical industry

(The question-marks stand for the specific tools to be identified during the empirical study.)

4.3.2 Second research question: the perceived relevance of the various tools

My second research question concerns how the perceived relevance of the individual resource-management tools in use compare *separately* in the original prescription only (ORX) and the generic prescription only (GRX) value chains. This research question is aimed at achieving the best possible understanding of the roles and the importance of the tools that can be used in the two business models *within the individual business models*. The research question is aimed at establishing the perceived relevance of the tools in use, so what I am after is how much significance the executives and specialists concerned attribute to the individual tools and solutions.

This research question has three explicitly formulated hypothesis linked to it. The first one concerns the preclinical phase of the original prescription only and the generic prescription only value chains and consists of the conjecture that in that phase – in both models – scientific and technological solutions play a more important role than either work organisation or business tools. The hypothesis is based, firstly, on the fact that it is in the preclinical phase that uncertainty concerning the future of the compound to be developed into a drug is the greatest, so resource allocation will be necessarily based on pharmacological, pharmaco-chemical considerations. So, according to my assumption, at that stage the answers to the question "*what shall we work on?*" are the definitive ones. Secondly, the decisions made during that period ma determine the entire subsequent process of pharmaceutical development, so particular attention is focussed on making the right technological decisions. The second part of the hypothesis reflects the fact that, presumably, the coordination of the various professions involved and the acceleration of working processes are already important challenges for management in the preclinical phase. Therefore I assumed that the executives of pharmaceutical companies would attach greater importance to those solutions than to business tools.

I have formulated Hypothesis H1 as follows:

H1. In the preclinical phase of the value chains, scientific and technological solutions have the greatest perceived relevance, with work organisation tools in second place and business tools coming last.

The second hypothesis concerns the clinical phase. My conjecture here is that the significance of scientific and technological solutions decrease, which is related to the path dependency I have mentioned above. In parallel, I expect the perceived relevance of work organisation solutions to increase, as they will allow the time and resources required for the clinical tests to be reduced. According to my hypothesis, the role of business tools will also be enlarged, primarily with the aim of ensuring that clinical trials and the licensing procedure are only carried through in the case of truly marketable molecules (i.e. those that meet existing healthcare demand and which are also financially profitable), both in the case of original and generic compounds. The dominance of the question of "what should we work on?" is eclipsed by these questions: "*Should we really work with it?*" and "*How can we accelerate it?*". Accordingly, my Hypothesis H2 is as follows:

H2. In the clinical phase of the value chains, the perceived relevance of scientific and technological solutions decreases while that of work organisation solutions and business tools increases.

The third related hypothesis concerns the period of the value chain that is subsequent to the placement of the drug on the market (i.e. the time after a licence is issued for the drug). My conjecture there is that business tools assume the dominant role in relation to both scientific and technological solutions and work organisation solutions. By that time, the fundamental processes of manufacturing and selling the drug are established and entrenched, but with the accumulation of market experience, the number of points of intervention for business tools increases. Accordingly:

H3. After going to market, business tools assume the dominant role in both value chains.

4.3.3 Third research question: differences between the original prescription only and the generic prescription only business models

My third research question concerns the comparison of the original prescription only (ORX) and the generic prescription only (GRX) business models. As the two business models differ in terms of temporal scope, risk-taking and resource-intensity, the relevance of the resource-management tools can be presumed to be different as well. It is possible that a particular resource management tool ha a high perceived relevance in a particular phase of the specific value chain of the generic prescription only (GRX) strategic model, for instance because the relative resource-intensity of that phase is high within the context of the entire generic prescription only value chain. However, the same tool may have only medium or minor relevance in the original prescription only model, in which the relative resource-intensity of the value chain phase in question is much lower. So we can assume that the perceived relevance of various resource-management tools differs in the two strategic models I am examining.

Therefore a comparison of the two business models appears to be justified. Due to the above considerations, my conjecture is that scientific and technological solutions and work organisation solutions will have lower perceived relevance in the generic prescription only (GRX) business model than in the original prescription only (ORX) model. The background behind that may be more moderate path-dependency, less technological uncertainty, smaller size of organisations, the omission of some tasks altogether, and the lower number of professions involved. Accordingly:

H4. In the generic prescription only (GRX) business model, the perceived relevance of business tools lags behind that of scientific and technological solutions and work organisation solutions to a lesser extent than in the original prescription only (ORX) model.

Finally, I also conjecture an additional difference between the generic prescription only (GRX) and the original prescription only (ORX) business models to the effect that in the GRX model, resource management after marketing of the product will be proportionally more significant than in the ORX model. So, in other words, my assumption is that while in the ORX model, the scope of action available after

marketing is largely already determined before going to market, in the GRX model this is not necessarily the case. The reasons for that are assumed to be lower path dependency and greater strategic flexibility. I have formulated this as a hypothesis as follows:

H5. Resource management after the product is placed in the market is more significant in the generic prescription only (GRX) business model than in the original prescription only (ORX) model.

The research questions and the associated summary hypotheses are provided in *Table 3* below, which is a repetition of *Table 1* from *Chapter 1*.

Research question	Summary hypothesis
1. What are the solutions available for increasing efficiency in the various sections of the original prescription only (ORX) and generic prescription only (GRX) value chains?	*This research question is aimed at gathering information, so it does not have any corresponding summary hypotheses*
2. What is the relative (perceived) relevance of those solutions along the individual value chains?	H1. In the preclinical phase of the value chains, scientific and technological solutions have the greatest perceived relevance, with work organisation tools in second place and business tools coming last. H2. In the clinical phase of the value chains, the perceived relevance of scientific and technological solutions decreases while that of work organisation solutions and business tools increases. H3. After going to market, business tools assume the dominant role in both value chains.
3. What are the main differences between the resource-management tools used in the original prescription only (ORX) and the generic prescription only (GRX) business models?	H4: In the generic prescription only (GRX) business model, the perceived relevance of business tools lags behind that of scientific and technological solutions and work organisation solutions to a lesser extent than in the original prescription only (ORX) model. H5: Resource management after the product is placed in the market is more significant in the generic prescription only (GRX) business model than in the original prescription only (ORX) model.

Table 3: Research questions and corresponding summary hypotheses of the dissertation (Repetition of Table 1)

4.4 Research methodology

Having taken to heart the critical comments of the reviews of the draft dissertation, I performed the research using a revised methodology relative to the one I originally envisaged. The hypotheses I have formulated do not favour a quantitative approach, so I performed qualitative research, based on in-depth interviews with pharmaceutical industry specialists and researchers working in adjacent branches of science who have direct experience of the processes of decision making in the pharma industry or who actually participate – or have participated in the past – in those processes in one form or another. In addition, I have also used other sources of supplementary information.

Pharmaceutical development and licensing takes part entirely outside Hungary in the case of companies adopting the original prescription only strategic model, and largely outside Hungary in the case of the generic prescription only model. As a result, I obtained information concerning the pharmaceutical development and licensing phases partly from executives working at international corporate headquarters and partly from consultants and researchers who are familiar with the mechanisms.

4.4.1 In-depth interviews conducted specifically for the purposes of this research

In order to write the present, final version of the dissertation, I conducted in-depth interviews with 14 persons. The most important methodological and background issues I need to make about the interviews are as follows:

- Of the 14 interview subjects, seven are of Hungarian descent and seven are foreigners. Of the Hungarians, six work in Hungary at present, but two of those have lived and worked abroad for extended periods of time in the past. One of my Hungarian subjects works abroad at present, at the headquarters of a multinational pharmaceutical company. Of the seven foreign interview subjects, two work in Hungary at present as the local managing directors of international companies, with one other subject who had worked in Hungary, while the remaining four have no connection to Hungary at all.
- Three of the interviews took place abroad, with eleven being conducted in Hungary. Of the latter, two were associated with the visits of subject living abroad to Hungary, while the remaining nine were organised specifically for the purposes of

the research. Of the three interviews that took place abroad, those conducted in 2009 were in-depth interviews of a "preparatory", orienting character that actually took place at a conference abroad in September 2009. After that, I suspended interviewing for an extended period (1 year) due to my high workload in my job and the writing of a textbook, then I conducted the remaining interviews between October 2010 and May 2011.

- My interview subjects were partly specialists who participate directly in international pharmaceutical development and market introduction projects as managers in charge of them, as consultants, or as internationally recognised scientists in the field. The other subset of the interview subjects consists of the managing directors of Hungarian subsidiaries of multinational pharma companies, who have a regional perspective on the main decision-making processes and who are the senior officers responsible for business decisions within Hungary, so they also have all the relevant business information related to the period after market introduction of drugs.
- The "corporate subjects" – of whom, not including consultants, there were ten – represent eight companies, i.e. I interviewed two people from two companies. Of those eight companies, six are in the original pharmaceutical industry (two of them also have generic portfolios), while two are purely in generics. This implies that the sample of companies is actually distorted to this extent towards companies in the original sector, but it must be taken into account that global generic pharma companies – which also conduct actual development and production rather than being simply "trade companies" are much fewer in number than global original pharma companies.
- I interviewed the Hungarian interview subjects in Hungarian and all the other subjects in English. Three of my foreign subjects were native speakers of English, so we may assume that they had a slight "language advantage".
- The length of the interviews ranged from 30 to 120 minutes, and in the case of three subjects I also had the opportunity to ask some additional questions by e-mail. The discussions were primarily related to the scopes of responsibility and competence of the subjects, so I discussed different issues with different subjects (see *Table 4*). Interviews nos. 11-13 constitute a separate subgroup in the sense that for those, I prepared English questionnaires that I sent to the subjects in advance, which

focussed on the issues of market access. With the other subjects, we did agree the subject of the conversation in advance by e-mail, but during the interviews we worked using the method of free association, i.e. starting with an opening question that was formulated quite generally (e.g. “What determines organisational efficiency [*in your area of specialisation*]? What are the solutions in use to improve it?), the subjects were encouraged to think freely and to “tell the story” of what they felt were the most important aspects.

- The methodology of the in-depth interviews may appear to be “slack”, indeed, at a few points it actually is, but when evaluating that fact it must also be taken into account that many of the subjects are overworked senior managers, so I had to view it as quite an achievement that they were able to fit such a conversation into their busy schedules at all. It was also an important circumstance to take into account that for the majority of the interview subjects, the jargon of economics and management science was foreign and difficult to comprehend (some of them would also have objected to it), while an informal tone (using everyday language) put them more at ease and allowed us to reach deeper insights. In addition, experience also suggests that the quality of the interviews conducted with the method of free association is no worse than those for which I sent questionnaires in advance: according to the three subjects that I did send questionnaires to themselves, only one of them actually looked at my questions in advance.
- When I compiled the list of 14 subjects I aimed to cover all phases of the pharmaceutical value chain, but despite my effort, some areas (e.g. quality management) are clearly underrepresented, while others (e.g. market access) are overrepresented in the interview material. When assessing that fact, it must be taken into account that due to the complex nature of the pharma industry, the specialists of individual areas have only limited knowledge of other areas, and that the managing directors of Hungarian subsidiaries primarily have direct access to information about government relations, marketing and sales, as they largely participate in the daily working processes of the companies in those areas.
- I shall use the main findings of the interviews in an anonymous form, without indicating the names of the companies or the subjects. The reason for this is that the majority of my corporate subjects specifically requested me not to include any references to the companies they work for. In view of that, the logical and consistent solution seemed to be to anonymize all the interviews and the references thereto

(even those with researchers and consultants). In Chapter 5, which presents the results, I referred to the conversations as *Interview 1*, *Interview 2*, etc.

The interviews are summarised in *Table 4* below:

Interview #	**Subject's nationality**	**Subject's position**	**Interview location**	**Main subjects of the interview**
Interview 1	Hungarian	(Previous) director, original pharma company, R&D centre	Hungary (2011)	Discovery, preclinical phase, clinical phase
Interview 2	Hungarian	Professor of clinical pharmacology	Hungary (2011)	Discovery, preclinical phase, clinical phase
Interview 3	Foreign	Professor of healthcare economics	Abroad (2009)	Discovery, clinical phase, marketing and sales
Interview 4	Hungarian	Director, generic pharma company	Hungary (2010)	Drug development, production (including logistics), marketing and sales
Interview 5	Foreign	Director, international headquarters of original pharma company	Hungary (2010)	Clinical phase, licensing, marketing and sales
Interview 6	Foreign	Director, international headquarters of generic pharma company	Hungary (2011)	Molecule development, drug development, licensing, marketing and sales
Interview 7	Hungarian	Senior economist, headquarters of original pharma company	Abroad (2009)	Discovery, preclinical phase, clinical phase, licensing
Interview 8	Hungarian	Managing Director, Hungarian subsidiary of original pharma company	Hungary (2011)	Clinical phase, licensing, production, marketing and sales
Interview 9	Hungarian	Managing Director, Hungarian subsidiary of original pharma company	Hungary (2011)	Licensing, marketing and sales
Interview 10	Hungarian	Managing Director, Hungarian subsidiary of generic pharma company	Hungary (2011)	Molecule development, drug development, production, marketing and sales
Interview 11	Foreign	Managing Director, Hungarian subsidiary of original pharma company	Hungary (2011)	Clinical phase, licensing, production, marketing and sales
Interview 12	Foreign	Managing Director, Hungarian subsidiary of original pharma company	Hungary (2011)	Clinical phase, licensing, production, marketing and sales
Interview 13	Foreign	Managing Director, foreign subsidiary of original pharma company	Hungary (2011)	Discovery, clinical phase, licensing, marketing and sales
Interview 14	Foreign	Director, market access consultancy firm	Abroad (2010)	Clinical phase, marketing and sales

Table 4: Main characteristics of the interviews conducted during the research

4.4.2 Other sources of information

In addition to the 14 interviews I conducted specifically for the purposes of this research, between May 2009 and March 2011 I also had several conversations with the directors of pharmaceutical companies as well as other experts that have yielded nuggets of information that I incorporated in my dissertation. Naturally, those may not be considered scientifically valid data and cannot be referenced, either, but they may be very significant and I was also able to use them while I conducted the interviews. Similarly, I was also able to draw on the knowledge and information I gained during my work as an expert concerning, directly or indirectly, the allocation of resources (e.g. business development decisions, decision associated with product promotion, decisions about strategy vis-à-vis regulators and financers).

I feel that some areas were not covered by the interviews. For those, I aimed to supply the missing material using secondary sources. During the period after I defended by draft dissertation, I reread the sources that presented case studies, illustrations and corporate solutions, and included that material with appropriate references in the appropriate sections of the chapter presenting the research results (*Chapter 5*), but I did not review additional literature at that time. The primary research (interviews) and the additional material from secondary sources are clearly defined and separated throughout, so the inclusion of secondary information does not interfere with the primary study and it does not deteriorate or indeed increase its value. On the other hand, the secondary information does make the overall picture more comprehensive and it has made the dissertation more "rounded off", more complete.

4.4.3 The method of presenting results

There are two distinct logics according to which the research results can be presented: on the one hand, it is possible to publish the results of individual interviews, on the other hand, it is also possible to follow specific value chains in accordance with the logic of the analytical model described in *Subsection 4.1*, and to describe the specific resource-management tools and solutions used in the individual phases in that sequence, indicating for each tool references for the interviews that were the source of the information about it.

In my opinion, the second approach is more expedient: it is more suitable for answering the first research question, and it is also a more systematic approach, which makes it easier to interpret the results. In contrast, discussing the results of individual interviews one after the other would fragment the subject, it would make forming an overall picture more difficult, what's more, the fields covered by the individual interviews varied, so they could not be compared directly.

Accordingly, in *Chapter 5* I shall proceed along the original prescription only and then the generic prescription only value chains, and I shall present the tools used, as revealed by the empirical results, and their relevance, in accordance with that sequence. For each phase of the process, I shall specify the interviews and, if applicable, the secondary sources that I derived the results from. My (systematising) conclusions concerning the hypotheses are provided in the summary *Chapter 6*.

5. Results

I will present the results about the resource management of original prescription only (ORX) manufacturers first (*Section 5.1*), followed by the results identified for the generic prescription only (GRX) strategic model (*Section 5.2*). In both sections, I shall attempt to follow the analytical framework outlined in *Section 4.1*. I will discuss resource management solutions that are associated with specific phases of the specific value chains first. Afterwards, I shall present the tools that are in use during several phases of the value chains.

5.1 Resource management along the original prescription only value chain

5.1.1 Discovery and synthesis

During the phase of drug discovery, the production of the target compounds requires significant material and non-material capacities (resources). They include the knowledge of pharmacologists, the tools and equipment, the IT systems with their various software packages as well as the required buildings, the raw materials and the supporting infrastructure. The cost of those resources – developer's salaries, material costs, depreciation, etc. – depends firstly on *the amount of time* it takes to produce the target compounds, secondly, *the hit ratio*, i.e. the number of useless molecules that are investigated before a useful one is found, and, thirdly, on the magnitude of the capacities made available (Interview 1, Interview 3, Interview 7, Interview 13). Taking all of those factors into account I suggest that efforts to influence the costs of molecular synthesis be grouped into three categories, as follows:

efforts may be aimed at

- reducing complexity costs by targeted selection of lead compounds (collectively referred to as *cross-section techniques*),
- reducing time-dependent costs by accelerating molecular synthesis (collectively referred to as *longitudinal techniques*),

- reducing the cost of the capacities to be allocated, through *outsourcing* or *rationalisation*.

5.1.1.1 Cross-section techniques

Cross-section techniques aim at improving the "output ratio" in the phase of drug discovery, thereby saving the company the cost of unnecessarily synthesised molecules that are unsuitable even for *in vitro* testing. These techniques are related to increasing the hit ratio and to searching for molecules in a targeted fashion.

Without exception, all cross-section techniques are **scientific and technological solutions**. One subcategory covers a set of related techniques such as *structure-based drug design*, *targeted design* and *virtual screening*. All of those techniques fall within *computer-assisted pharmacological research*. Structure-based drug design allows molecules to be associated with specific biochemical properties and to model them using computers. Targeted design helps with developing a drug molecule that fits the biological receptor involved. Virtual screening is the screening of computer models of libraries of compounds that also exist physically, i.e. the screening of virtual compound libraries. The task is to identify molecules that are active against the target protein, and to reduce the range of compounds to be screened before commencement of physical screening (Interview 1, Interview 2, Interview 3, Interview 13).

My interview subjects felt that the *relevance* of computer-assisted drug design was high, primarily due to its high *potential*. Modelling allows the elimination of expenses whose superfluity would only have been discovered in earlier times after performing the tests. The simulation software packages are expensive, but they simplify compound research to such an extent that their overall effect on costs is clearly positive. They have the added advantage of freeing up the resources that would otherwise be employed in investigating "barren" compounds, which means they can be put to productive use instead. *Implementability* is difficult to assess in general. My interviewees described organisational situations in which the introduction of virtual techniques met with resistance from the specialists, while they also emphasised that there are significant differences of opinion between the researchers on this, but "in the final analysis, the decision will be made by the party with the money" (Interview 1). There are rarely any

doubts about the intuitive character of the software packages, but researchers often question the authenticity of the results. What's more, learning to use the software takes time, and acceptance of the new techniques can only be expected after that process is completed (Interview 3, Interview 13).

The other subcategory of cross-section resource-management techniques consists of exploiting the opportunities of *pharmacogenomics*. Pharmacogenomics is the subfield of drug research that seeks to find drugs to cure genetic diseases on the basis of the human genome and genetic differences between individuals. By building a bridge between genetics and pharmacology, it makes drug research more targeted: it helps with the identification of therapeutic targets and the targeted design of drug molecules. Based on experience so far, the interviewees believed that the *relevance* of pharmacogenomics was medium, with some of them believing that the revolutionary breakthrough that was expected in the 1990s did not happen and it is not likely to happen within the next ten to fifteen years. Personalised medicine is still in the early stages today, what's more, for the time being, pharmacogenomics is only prepared to deal with monogenic diseases only – pharmacological therapy for diseases attributable to the simultaneous malfunction of several genes is as yet uncertain, particularly as regards the avoidance of side-effects (Interview 1, Interview 5). Based on the responses to my questions, the *implementability* of pharmacogenomic solutions is difficult to assess as yet, but it is already clear that it will require specialised competencies and professional procedures relative to both chemical drug synthesis and biotechnological drug research, so it is mostly used only by specialised research companies and academic workshops (Interview 1).

5.1.1.2 Longitudinal techniques

Longitudinal techniques work through reducing the time requirement of molecular synthesis and most of them are largely technological in character. The initiatives that attempt to make organisational or management changes are less significant.

At the present state of scientific knowledge, **scientific and technological solutions** of this type belong in the areas of *screening methods* and *combinatorial chemistry*. The best solution for accelerating molecular synthesis is to replace the long and costly monophase synthesis by processes that generate many new compounds in a short time. The

procedures of combinatorial chemistry do that, but they can only provide a real advantage if the large quantities of various compounds that they create in a mixture can be separated in an economical manner. So combinatorial chemistry can be an effective technique for increasing efficiency if it is used in conjunction with high throughput screening (HTS) techniques and strong IT support (Interview 1). The other – increasingly important – task of screening techniques is to search existing compound libraries for potential candidate compounds once a new molecular target is identified (Interview 1).

In conjunction, combinatorial chemistry and high throughput screening allow up to several million compounds to be produced and tested in a year, at a much lower cost. For instance, the cost difference between screening a few ten thousand or a few hundred thousand compounds is negligible (Interview 1, Sweeny [2002]). The expected effect is reduced by the fact that the structural range of molecules that can be tested in a single screening test is limited, and the results are influenced to a great extent both by the quality of the compounds (in the worst case, they can be random) and the screening algorithm to be used. Finding the right screening parameters usually takes more time than the screening itself. The effect of the technique is also reduced by the fact that sooner or later, real laboratory testing does become necessary (Interview 1).

According to the opinion of the experts I asked, the *relevance* of the screening and combinatorial chemistry methods is very high (Interview 1, Interview 2). That very high relevance is primarily the result of their great *potential*, partly because the potentially available strategic advantage is very large and partly because they act on a phase of the process that is extremely resource-intensive. In addition to the direct savings on costs, they also give rise to competitive advantage in the market. According to the interviewees, the relevance of combinatorial chemistry is constrained by its relatively difficult *implementation*: a great deal of equipment and IT background is required, so entry costs – including the education and training required – can be high.

Work organisation solutions include the acceleration of the working process without changing the technological boundary conditions through more efficient organisation of work and better management of raw materials. The *relevance* of those techniques is minor relative to the scientific and technological solutions, primarily because the costs

of molecular synthesis are technology-dependent, so the proportion of resources that can be influenced is low, and accordingly the expected effect and *potential* are also low. Secondly, *standard operating procedures* (SOP) prescribe precision and make minor changes intrinsically uneconomical. The role of management is largely limited to setting and enforcing performance targets (Interview 1, Interview 3).

The *implementability* of work organisation solutions is the function of several factors: the researcher mindset is not in favour of excessive regulation, but considered suggestions from management can help researchers achieve an optimal degree of organisation. However, experience with development departments shows that the people working there often find the performance measurement and performance assessment initiatives coming from above incomprehensible and they tend to see them as "meddling by the suits" (Interview 1, Interview 3).

Corporate management does set targets and verify their achievement in the research and development phase, too. One example is an international company doing original drug research that sets cost targets in its annual plan for the various research sections, but it does not specify the means by which those targets are to be met. The heads of the sections decide the manner in which they wish to (and are able to) achieve the required improvement (Interview 3).

According to my results, none of the longitudinal techniques in use are **business tools**.

5.1.1.3 Reducing the cost of capacities

The necessity of reducing the cost of capacities arises in relation to drug research, too, particularly as a result of the deterioration in the efficiency of producing new active compounds. The leading pharmaceutical companies doing original research do not have sufficient numbers of *blockbuster* or *nichebuster* drugs to finance their in-house research and development projects at the previous capacity levels. According to my interviewees, during the phase of molecular synthesis, there are two available avenues for reducing the cost of capacities: outsourcing and rationalisation. Both of those constitute **work organisation solutions**.

Of those two techniques, the *outsourcing* of tasks associated with drug research is the less painful decision. Outsourcing may be comprehensive, in which case the production of active compounds is taken over by so-called contract research companies; but it can also be partial, in which case the parent company and its external partners establish joint projects or ventures in order to make research more efficient. In addition to the reduction of fixed costs and performance-based fees, outsourcing is also favoured by the fact that the expertise, technological superiority, flexibility and willingness to take risks of external companies specialising in particular fields may be greater, as a result of their smaller size and greater concentration of capacities (Interview 1). It is an incentive to outsource if the resources thereby freed can be used more efficiently in other areas (Interview 3, Interview 7, Interview 13). *Relevance* is high, but lower than that of the scientific and technological solutions mentioned among longitudinal and cross-section techniques, and it also exhibits greater variability. *Potential* is primarily the function of the part of research work that can be outsourced and the extent and nature of the effect that such outsourcing has on the company's strategic capabilities. The *implementability* of outsourcing is uncertain: it is primarily the function of the area in which the resources freed by it are to be utilised. The level of acceptance between the internal and the external participants and the degree to which their different cultures and interests can be reconciled are important and difficult issues (Interview 1, Interview 7, Interview 13).

Rationalisation can occur using various methods and with various intensity. In the experience of my interview subjects, it may involve across-the-board reduction of research budgets, which is decidedly harmful, or differentiated interventions, which are more difficult to implement but also cause less harm. Rationalisation is often accompanied by down-sizing and the closing of research facilities – this is particularly characteristic after fusions or the establishment of *excellence centres*, when companies aim to eliminate parallelisms (Interview 7, Interview 13). The *relevance* of reducing capacity costs is difficult to interpret in general primarily because *potential* is a function of an exceptionally large number of factors – strength of the strategic approach, degree of rationalisation, period of time, and so on. Looked at from a longer-term perspective, rationalisation is beneficial if it reduces uneconomical development capacities while leaving productive capacities unchanged. In addition to the corporate management tactics used, *implementability* is also dependent on the amount of tacit knowledge that is wasted as a result. Sentiment against rationalisation is usually strong, options for

creative participation are limited, the range of people concerned is wide, while communicability varies from target group to target group as a function of vulnerability to uncertainty. All in all, it still seems that rationalisation based on the across-the-board principle is easier to implement (Interview 1, Interview 7, Interview 13).

5.1.2 Preclinical trials

Preclinical trials are costly due to the large variety of the resources consumed: the salaries of researchers are a significant item along with laboratory equipment, experimental materials, and the laboratory animals themselves are very costly as well. The cost of the supporting infrastructure is significant due to the room required for the trials, the computers required and the documentation requirements. All in all, preclinical trials are highly cost-intensive, partly exacerbated by the strict regulatory framework (GLP). The resources of the preclinical phase can be managed in a similar manner to the costs of molecular synthesis. According to the results of the interviews as well as secondary sources I suggest the following classification:

- Acceleration of trials and discovery of risks as soon as possible (*frontloading*)
- Outsourcing of trials to external partners
- Resource management extending beyond the preclinical phase

5.1.2.1 "Frontloading"

According to the results of the interviews, the acceleration of trials and the early identification of risks is facilitated – similarly to the molecular synthesis phase – by either scientific and technological solutions, which have high relevance, or work organisation solutions, mostly with medium relevance.

The **scientific and technological solutions** in use include in silico testing, trial design and parallel testing. The essence of *in silico tests* is that bioactive molecules are tested on computer models of the human organism for toxicity and biological utility before trying them on tissue cultures or animals. Thanks to *in silico* models, a significant part of the costs is accumulated in the early part of preclinical trials, which reduces the possibility of only finding out that a particular molecule is toxic years later, in the late

stages of animal testing. Computer toxicity testing therefore converts future costs to present costs.

Trial design can be performed on a computer or "in the head". Computerised trial design aims to optimise the subsequent phases of the trials using project management tools, simulating high-risk (high failure rate) trials virtually or in vitro as soon as possible (Interview 1, Interview 2, Berressem [1999]). This ensures that only compounds worth the trouble reach the highly resource-intensive in vivo trials.

Parallel testing occurs in the animal trials phase. Its purpose is to reduce the number of laboratory animals required and the period of time required for observation by using a single animal to test several compounds. In essence, the method involves delivering several different molecules to the animal's organism at the same time, then using structural exploration methods and the regular control of the serum level of the compounds to draw inferences about the toxicity and biological utility of the individual molecules (Interview 1, Berressem [1999], Curry [2002]).

According to my interviewees, the *relevance* of scientific and technological solutions is very high, due to the high *potential* resulting from the opportunity to save time. It is practically impossible to overestimate the significance of the cost reductions that may be afforded by computerised procedures and parallel testing. But the therapeutic field affects the potential of procedures of a technological nature for two distinct reasons. On the one hand, the medicines proposed for certain psychiatric syndromes are not possible to test on tissue cultures or computer simulations – in those cases, in silico and in vitro trials are only suitable for testing toxicity at best (Interview 1, Interview 7). On the other hand, certain groups of diseases (cancers, leukaemia, metabolic disorders etc.) can only be treated using drugs that may have hazardous side-effects, so they require particularly thorough and lengthy animal trials (Interview 1). The *implementability* of computer-assisted procedures is subject to all the constraints I have already mentioned related to computer-assisted compound design: researchers may favour non-virtual trials and it takes time until they become sufficiently capable users of the software.

Due to the complexity of preclinical trials, the *relevance* of **work organisation solutions** – better task planning, more efficient material management, etc. – is greater

than in the molecular synthesis phase, overall it is of a medium level. Everything else I have already said about those solutions is also applicable to preclinical trials.

5.1.2.2 Outsourcing of preclinical trials

The outsourcing of drug discovery tasks (which is a **work organisation solution**) is considered routine these days. The outsourcing of preclinical trials is also becoming more common, but most of those are still performed in-house. The reason for that is partly that some of the companies consider the trials to be a part of their strategic learning process. Secondly, the regulations applicable to preclinical trials are so strict that performing the task in-house is actually a guarantee of quality. Thirdly, the technology and performance of preclinical trials is a component of the company's strategic capabilities and may involve several patent aspects (Interview 1, Interview 7).

Despite those constraints, the outsourcing of the preclinical phase does offer significant benefits, and the large pharmaceutical companies are increasingly waking up to this fact. They are particularly likely to use external partners for the testing of compounds with biotechnological significance, or which are outside the mainstream of their research, or whose chemistry is in a field in which the company is at a comparative disadvantage. In such cases, the preclinical trials are performed by the external partner that developed it. Many biotechnology companies offer integrated molecular synthesis and preclinical trial services to pharmaceuticals (Interview 3, Interview 7).

The *relevance* of the outsourcing of preclinical trials is medium in comparison with the totality of techniques available for managing the resources of preclinical trials, while it is difficult to assess its *implementability* at all in a general sense. When we look at the details, it is a function of factors such as the fate of strategic assets, the opportunities for utilising the resources freed up and the reduction of development risk achieved. In the case of partial outsourcing (cooperative efforts), cultural factors and problems of conflicting interests must also be taken into account.

5.1.2.3 Resource management extending beyond the preclinical phase

The future form of dosage and production technology of the potential drug is best determined – at least approximately – in parallel with the preclinical trials. The branch of pharmacological development concerned with production technology, *process chemistry*, which is a **scientific and technological solution**, is halfway between the nitpicking finance divisions, always bent on economic rationality, and the researchers, who are wont to be impressed by scientific wonders but are less sensitive to costs. Its task is to facilitate the production of drug compounds on an industrial scale. The basic outlines of the production process need to be designed when the drug is still in production, so as to ensure that any problems with scaling up and producibility come to light in good time. It is possible that the industrial-scale synthesis of a compound is disproportionately expensive relative to its earning potential, or that minor structural modifications are required in order to render the compound producible at all. Process chemistry examines all the possible production pathways suitable for mass production and determines which are the ones whose costs are within a justifiable limit. In some cases, it seeks the cheapest and fastest technology to start with – regardless of the cost.

The most important task of process chemistry is therefore to find production pathways that are safe, which produce perfect quality and which can be implemented in the target plant. These processes must consist of subsequent steps of synthesis that are cheap and fast, with highly productive reactions, for which raw materials are easily available at a favourable price, easy to manage, and which are characterised by exploitable economies of scale and no bottlenecks that would render industrial production impossible (Interview 1, Interview 3). At a given level of technology, alternative production pathways can be defined and prioritised clearly, but after the optimal path is selected, the possibilities of process development become severely constricted.

Although it is not necessarily a process chemistry issue, *the selection of the production site* is related to the development of production technology in several respects, at least in the case of multinationals. When an international company is making a decision about which plant to produce its new product at or where to establish new production capacity for the product, the most important decision factors are the proximity of the target market and the minimisation of logistics costs (Interview 3, Interview 7, Interview 13). However, the place of production can influence process chemistry in the sense that despite increasing international harmonisation, there are still differences between

individual countries as regards regulations and environmental provisions, while among production management factors, optimal plant size is the primary one that is a function of location.

The *relevance* of process chemistry is high (Interview 1). On the one hand, it avoids cost items that would otherwise be incurred over and over again over the many years of production, while on the other hand it can generate a competitive advantage for the company, either through process patents or through increasing the efficiency of production. However, its prevailing *potential* is highly dependent on the target therapeutic area: some areas require complex drugs that are difficult to synthesise, with few alternative production methods available. The *implementability* of process chemistry is at its best if it is based on cooperation between research chemists and production engineers (Interview 7, Henry [2002]). In such cases, both groups play a role in developing the tasks, inter-group communication becomes smoother and the fear of researchers that production engineers are trying to take over some of their work is alleviated.

5.1.3 Clinical trials

During clinical trials, resource allocation may only be optimised using ethically impeccable means that are also approved by the regulatory authorities. However, according to my interviewees, the possibilities approved by the authorities leave some room for manoeuvre. According to my research, these possibilities (or, in fact, "necessities") include "phase 0" and *proof of concept* (PoC) tests, limited registration, close cooperation with the regulatory authorities, structured selection of patients, the careful selection of the trial design and sites, the use of data management and communication technologies, strategic pricing and project management (Interviews 1-3, Interview 5, Interview 7, Interview 8, Interviews 11-14).

The techniques listed are primarily **work organisation solutions**, but phase 0 and proof of concept tests, the structured selection of patients and the earlier start of effectiveness tests also include some **scientific and technological solutions**. Strategic pricing and project management, which are **business tools**, will be discussed among techniques that

are in use over several phases of the value chain (*Section 5.1.7*), while I shall discuss the other techniques below.

The purpose of phase 0 and "*proof of concept*" studies is to minimise the inherent risks of clinical development, in particular to ensure that the decision as to whether the development is to be continued ("*go/no go"*) is made as early as possible (Interview 1, Interview 2). It is a fundamental principle of clinical studies that if the effectiveness of a molecule comes into doubt, the molecule is to be forgotten straight away. The exclusive objective of phase 0 studies is to test whether the drug is active in human subjects in the way that was expected on the basis of animal testing. In phase 0 studies, the dose administered is so low that it can have neither medicinal nor toxic effect. These tests allow an earlier assessment of whether the molecule has any pharmacological properties that justify later trials on large numbers of patients (Interview 2, Interview 14). The term *proof of concept* indicates that during phases I and II of the clinical trials – with several iterations, if required – the indication and patient population for which the effectiveness of the drug is acceptable, preferably not only relative to placebo but also to existing therapies (*comparative effectiveness*) is found. The development of the drug is continued only if the preparation has proven therapeutic added value relative to existing therapies, or if it is at least not inferior to them (Interview 2).

So-called *limited registration* is closely related to *proof of concept* studies. It means that the new drug compound is optimised for a narrower registered indication, which ensures earlier access to market. After registration, indications can be extended gradually during the period when the product is already generating revenue (Interview 1, Interview 2).

Close cooperation with the regulatory authorities represents investment in speeding up communication and in ensuring that no unexpected obstacles are encountered during the most costly phases of clinical trials. Cooperation with the regulatory authorities helps avoid those errors in clinical trials that, according to experience, are the more likely to result in a failure to licence the drug. They are as follows: incorrect choice of dose or method of administration; weakness of the statistical methodology used; an observation period that is too short; insufficient randomisation techniques and/or test methods, problems related to the "blindness" of the trials; deviation from the test record. In addition, cooperation can also help to prevent loading the test documentation with large

quantities of data that the authority does not actually require (Interview 5, Interview 7, Interview 14). In the United States, the FDA issues guidelines for clinical trials that companies are required to observe; in return, if the results are compliant, registration is performed without any obstacles. In Europe, the EMA consults with the manufacturer, but the exact script for the test is developed by the manufacturer, and the authority only assesses it afterwards, so there is more uncertainty in the registration phase (Interview 2).

The *structured selection of patients* is highly significant in phase III clinical trials, the multicentre trials, particularly because regulatory authorities are demanding increasingly large and independent trial populations (Interview 2). The reason for that is that in various parts of the world, the characteristic supportive or standard clinical therapies may differ and there may also be differences in the genetic makeup of patients and hence the course that diseases take, and the social acceptance of the pathology concerned may also vary. Therefore regulatory authorities may expect the sample to cover several geographic regions. The selection of patients has been a problematic feature of clinical tests, according to a survey conducted by the organisation *CenterWatch*, it is responsible for at least one in four delays (Watkins [2002]). It is difficult to obtain test subjects for a number of reasons: the complexity of the pathologies, individual aversions towards the unknown and the objective parameters of patient selection (largely biological parameters) all play a role in this. The recruitment of patients and achieving the required numbers can be rendered easier if the company – while observing the regulations applicable to the data – has detailed health, demographic and ethnographic data about all the parts of the world; if it maintains a relationship with a network of trial centres, and if it used the opportunities afforded by the internet (Interview 2, Interview 5, Interview 7, Houghton [2002]). It is of key importance that the company should establish a network of “feelers” and advocates consisting of doctors, marketing specialists and clinical trial organisers whose networks and knowledge of the market assists them in recruiting patients (Interview 14).

The active ingredient Imatinib, for the treatment of certain varieties of leukaemia, was registered in 2011. Prior to the clinical testing of the drug, the manufacturer company disseminated the message that the trials would be started to a wide range of people, so patients began to approach the company themselves – the problem of recruitment was thereby solved. Of course, the case was not a typical one, as the onslaught of

patients was partly due to the fact that the illness is fatal. Nevertheless, the manufacturer concentrated the majority of expenditure on the early phases of clinical testing in order to reduce the risk. Another large pharma company aims to structure the patient selection process by analysing the genetic data of patients who had participated in its previous trials, as an attempt to discover which drugs are best tested on which groups of patients (Watkins [2002]).

The *trial configuration and selection of sites* partly has the same aim as the structured selection of patients, i.e. it accelerates the process and reduces the cost of establishing the trial infrastructure, while on the other hand it helps to screen out trial centres of dubious quality, reliability or prestige. As regards trial configuration, innovative (alternative) trial methodologies that yield valid results with less patients and shorter observation periods are continuously being published (Interview 2). The proper selection of sites is primarily related to quality assurance in the wide sense, its techniques include audits and the certification of clinics and the evaluation of experience obtained previously. The establishment of a balance between costs, infrastructural conditions and the complexity of the trial is also a factor (Interview 2). Careful selection of trial locations is also critical in the sense that in some countries, the commencement of Phase I trials only requires a summary of the preclinical trials and substantial evidence, but the authority does not require submission of detailed statistical tables. This can result in a significant saving of time (Interview 5, Interview 7, Interview 14).

The selection of clinical locations is influenced by the markets that the company wishes to place its new product in. The United States, Europe and Japan are usually indispensable. For a long time, the prestige of clinical trials decreased from north to south: it was the highest in Scandinavia, followed by Great Britain and Germany. France was also good, and Italy had acceptable prestige. The significance of the Central European region has become definitive due to low costs and a reliable standard of quality, but the number of trial clinics in developing countries is also growing (Interview 14).

Data management and communication technology refers to the systematic application of the tools of information technology and process automation in the interest of coordinating partial projects and partial processes. For the companies, producing, collecting, organising, processing, evaluating, auditing and validating the results of clinical trials is a large burden, and they also need to coordinate the resources, activities and processes that support the trials. Document management, process management, decision support, simulation and other IT tools provide assistance with those tasks

(Interview 5, Interview 7, Interview 8). They have the significant advantage of saving a great deal of time, as they can reduce the number of communication loops, for instance by allowing the consistency and proper completion of the trial data sheet to be verified in real time. It is a further advantage that they also allow personnel and travel costs to be reduced on the side of the trial manager and the monitor (Interview 2).

All in all, the interviewees felt that the *relevance* of the resource management techniques of the clinical trial phase was high, or even very high in the case of some techniques. It was primarily the proof of concept approach, limited registration, structured selection of patients and the selection of trial locations to which they attached particularly high relevance. Of the components of perceived relevance, *potential* is increased if the company is performing the drug development of some product – even an intermediate product – for *someone else*, and that someone else happens to be the registration authority (Interview 5, Interview 7, Interview 14). So it is no accident that it is in that phase that the emphasis is really placed on the productive costs of quality and compliance. Potential is also increased by the fact that during clinical development, a number of partial processes which are distributed in space and time, which have a variety of functions and uncertain outcomes, need to be coordinated (Interview 8, Interview 14). On the other hand, potential is reduced if clinical trials are strongly dependent on the regulatory environment and the conduct of the authorities that supervise the clinical trials. The majority of the changes planned require approval of the supervising authorities, and informal communication is always required (Interview 5, Interview 7, Interview 8).

The specific therapeutic area can have a multiplicity of effects on the perceived relevance of the techniques listed. Some families of drugs may prove ineffective in a significant proportion of patients due to genetic reasons (Interview 1, Interview 2, Sweeny [2002]). In such cases, the time and cost requirement of the clinical trials increases, and among the above techniques, only the structured selection of patients is suitable for reducing the effect. Secondly, it is much easier to get test subjects and testers for trials involving drugs that promise a therapeutic breakthrough or which are particularly important for humanitarian reasons (Watkins [2002]). Thirdly, some therapeutic areas (central nervous system, cardiovascular system, hormones, etc.) and groups of drugs are more complex or problematic than others, so they require more tests and more strictly monitored clinical trials (Interview 7, Interview 8). All of those factors also affect the relevance of various resource-management tools.

In the opinion of my interviewees, the *implementability* of the above techniques is largely dependent on the willingness of external participants to cooperate. The attitude of the clinical testers and the drug authorities is paramount. The implementability of a smaller part of the techniques – in particular, information technologies – is also dependent on the attitude of internal stakeholders, but that does not give rise to significant problems. The actual specific relevance and expected effectiveness of the resource management tools belonging to this phase are provided in the table about original manufacturers in the *Appendix*.

5.1.4 Licensing and obtaining public funding

During the licensing phase, the authorities may require supplementary information, additional details or explanations from the pharmaceutical companies, and they are also required to take the initiative and correct any defects of content of form of the trial documentation (Interview 5). As the majority of drug administrations work in accordance with entrenched standards and in accordance with a predictable logic, pharmaceutical manufacturers can understand their ways of thinking and thereby realise significant savings of time (Interview 5, Interview 8, Versteegh [1997], Woodcock [1997]).

As a result, the most important resource management tools that my interview subjects mentioned for the licensing and public funding phase were *consultations with the regulatory and financing authorities* and the *key account management* system that has been established to replace ad hoc lobbying (Interview 5, Interviews 7-9, Interviews 11-13), which mostly belong in the category of **work organisation solutions**. During the time while the registration and financing documentation of a drug is under review, it is expedient to clarify any disputed issues as soon as possible and to deal with potential official objections in a proactive manner. This allows the additional work resulting from the repetition of some phases and the supply of missing items to be avoided.

As the licensing process becomes increasingly strict, the *expenditure requirement* of licensing and obtaining public funding also increases, but my interviewees still felt that the *relevance* of resource management in this phase was only medium relative to the entire value chain. During this phase, which is very close to the market, the

manufacturer is primarily driven by marketing issues, attention is focussed on putting the drug in the market as soon as possible, so considerations of efficiency do not play a role. The therapeutic area concerned influences relevance during the licensing phase inasmuch as the authorities tend to conduct the administration of drugs for rare diseases or those that are important due to humanitarian reasons faster (Interview 3). *Implementability* is primarily influenced by the registration authority and the financer, but and manufacturer is only able to influence them informally with the objective of speeding up the licensing process or to reduce official costs.

My results indicate that during the licensing phase, **scientific and technological solutions** and **business tools** do not have a role. It should be noted, however, that the techniques of strategic pricing and project management, both of which are used in several phases of the value chains, are in use during the licensing phase as well (see *Section 5.1.7*).

5.1.5 Production

The direct production costs of drugs are low relative to the sale price, but the margin is not pure profit: it covers future developments in the same way that the margin of previously marketed drugs covered the development of present products. Looking at the matter in greater detail we also discern that the cost of production is only low relative to development and marketing costs (Interview 8, Interview 11, Interview 12). In actual fact, the margin indicators of pharmaceutical production are quite unfavourable: a small quantity of finished product requires a large amount of raw materials and auxiliary materials. During the production phase, resource management focuses on the cost-efficient procurement and management of those raw and auxiliary materials, the optimisation of production capacities and on streamlining the supporting infrastructure; the use of techniques associated with production in the narrow sense (manufacture of active ingredient and formulation) is limited. Therefore, **work organisation solutions** play the primary role, which is due, firstly, to the fact that, thanks to process chemistry, industrial-scale manufacture already begins with the most favourable of the known technological pathways. Major changes are only required if, during the learning process, the possibility of innovation arises that can be implemented in an economical manner despite the costs of registration, redocumentation and additional training. On the other

hand, the regulations governing quality management and environmental protection also greatly reduce the range of production costs that can be influenced (Interview 7, Interview 8, Interview 11, Interview 12).

However, in addition to work organisation methods, business tools also play an important role: particular techniques include the streamlining of the support infrastructure by process management, multilevel planning, performance indicators and cost calculation (Interview 7, Interview 8, Interview 11). I note that process management also involves some work organisation solutions.

5.1.5.1 Optimisation of activities associated with procurement and inbound logistics

Among the resource-management tools associated with procurement and inbound logistics, which belong among work organisation solutions, procurement process optimisation, maintenance of high procurement quality and establishment of optimal stock levels play particularly important roles (Interview 8, Interview 11, Interview 12).

Procurement process optimisation can be interpreted as the simplification of the flow of materials and documents between suppliers and the manufacturer. Within the framework of production organisation, process optimisation must begin with batch sizes and frequencies, and the opportunities afforded by information technology should also be utilised. The work is rendered easier by the fact that original pharmaceutical factories usually maintain long-term relationships with their suppliers, so streamlining the procurement process is in the interest of both parties. On the other hand, progress is rendered more difficult by the fact that not all suppliers are ready for paperless cooperation (Interview 11, Interview 12).

The *maintenance of high procurement quality* is a cost prevention technique related to quality management. Good manufacturing practice (GMP) contains strict regulations about the characteristics of the materials to be used. For instance, if the packaging of an incoming material is damaged, the material is returned to the supplier, but the associated procedure ties up the pharmaceutical factory's resources. If, at any control point, it is found that the materials used are not compliant with *all* provisions, the product in production has to be destroyed and the event has to be documented carefully. So non-

compliance has a double cost: it is composed firstly of the cost of the materials and work that are wasted, and secondly of the time that the rectification and documentation of the problem requires. The best was to avoid incurring non-compliance costs is to demand perfect quality of supply, to conduct regular customer audits and to place cooperation on a “voluntary” basis (Interview 8).

The *establishment of optimal stock levels* is a natural incentive in order to reduce the quantity of resources tied up in raw materials. The optimal levels of stocks – similarly to the characteristics of the procurement process – are a function of the production programme developed during production organisation. They are influenced by the size and frequency of batches, their processing time, raw material requirement, the conditions for purchasing the raw materials (quantities that may be ordered, frequency of ordering, packaging sizes, discounts, etc.) and the expected level of safety backup stocks.

According to my results, the majority of the techniques listed above have medium *relevance* relative to the entire value chain. Although “clearing out” unnecessary stocks and preventing quality problems can result in significant savings, the resulting *potential* is dwarfed by the benefits of accelerating market access. *Implementability* is good; according to my interviewees, the strongest limiting factor on it is that pharmaceutical factories tend to avoid upsetting the *status quo* in any case that also affects GMP. The direct and indirect costs of validation and documentation – including labour, the entrenchment of new practices and the costs of any problems that may arise – reduce the willingness of manufacturers to introduce changes considerably.

5.1.5.2 Optimisation of production capacities

The optimisation of production capacities – which is also a work organisation solution – gains significance because in the original pharmaceuticals industry, the level of utilisation of fixed assets is low (Interview 8). As there are rarely opportunities for minor improvements and iterative process development, the management of production capacities is conducted using more drastic interventions. Such interventions include outsourcing, rationalisation within the plant and the concentration of production capacities at larger facilities.

Outsourcing usually targets active ingredient production or packaging (Interview 11, Interview 12):

- The *outsourcing of active ingredient production* had its golden age in the second half of the 1990's, but more recently, there are certain signs of *in-sourcing* as well, particularly at companies that were unable to get rid of the infrastructure of their outsourced units (Interview 8). The outsourcing of active ingredient production is practically a necessity of the pharmaceutical manufacturer has also outsourced preclinical tasks previously. It is often the company that performed the previous tasks that gets the outsourcing contract for active ingredient production (Interview 11, McCoy [2002]). Most manufacturers of original drugs require their partners to synthesise the active ingredient under an exclusive contract, only for them. However, after the patent on the active ingredient expires, it often happens that the same company supplies both the original and generic manufacturers in bulk. It can be considered a disadvantage of outsourcing that the long-term interest of the external partner is weaker than in the case of in-house production, while maintaining the same standard of quality may require regular customer audits, with significant extra costs (Interview 11).
- Few manufacturers consider the *packaging of final products* to be a part of their core competency; establishing the optimal weight and volume and the safe but economical and recyclable packaging material is easier for a packaging business (Interview 11). The packaging manufacturers themselves aim to shorten or eliminate internal transport routes and to reduce the range, weight and volume of the packaging materials used; they are automating everything that can be automated; finally, they produce standard loading units to optimise transportability (Interview 11, Interview 12).

According to the testimony of my interviewees, the relevance of outsourcing is of a medium level for the entire original prescription only value chain, with the primary reason being that production costs contribute a relatively low proportion of the cost of original drugs, and that the cost structure was already determined during the development of the production technology. So, looking at the entire value chain, *potential* is not particularly high. (Interview 11, Interview 12).

The considerations applicable to in-plant *rationalisation* and the *concentration of production capacities* are similar to those I described in relation to across-the-board and differentiated rationalisation in *Section 5.1.1.3*, with the provision that my results suggest that in the production phase, the potential and relevance of those techniques is low or medium (Interview 8, Interview 11).

5.1.5.3 Streamlining of the support infrastructure

In the support areas – whose consumption of resources was difficult to track for a long time – a business tool, *process management* has gained the forefront recently. Among the resource-management tools listed so far, this is the one that is perhaps the least industry-dependent: it is usually implemented using integrated corporate management systems and its central feature is a technique of cost calculation – process cost calculation or activity-based cost calculation. Processes involving several functional units (material management, facility operation, maintenance, environmental protection, quality assurance) are tracked in order to assist with mapping the "resource flows" within the company, to identify unnecessary or poorly organised activities, to take remedial measures and to perform planning (Interview 11, Interview 12).

The majority of companies realised the role of process management during the nineties: that was when they finally arrived at the realisation that it is not only production, but also supporting production that costs money, and those costs can be influenced. But even in view of all those considerations, the perceived relevance of process management is medium over the entire value chain (Interview 8, Interview 11, Interview 12): although the costs of support processes are easier to influence than those of production costs, relevance is reduced by the fact that in the original pharmaceuticals industry, process management in itself does not generate a strategic advantage, which means that it has medium *potential*. Its *implementability* depends on the extent to which the essence and benefits of the process approach is communicated successfully to those involved, including the fact that this requires the horizons of support units to extend beyond their physical boundaries. As process management is generally model-dependent (it is usually introduced through consultant projects), the management literature has a great deal to

say about the factors that influence the quality of implementation[28]. The thing I wish to emphasise here is that reducing the number of levels in the organisation and increasing personal responsibility is in most cases sufficient to increase the commitment and long-term loyalty of medium management (Interview 11).

5.1.5.4 Other business tools

According to the results of my research, in the production phase, the business tools usually classified among so-called controlling tools in the management sciences also play a substantial role. They include multi-level planning, costing methods and performance indicators. All of the specialists I asked about production (Interview 8, Interview 11, Interview 12) reported that their companies do use these tools in the area of production, and that they have a fundamental effect on daily operation. Batch cost calculation, the indicators prescribed by GMP and production planning are particularly important. My subjects felt that the relevance of those tools was medium for the entire value chain. In it interesting and revealing that I had an interviewee who attributed the low penetration of business tools at his own company to the poor presence of consultants, which is experienced by the company as the strategy of "protection against superfluous fads" (Interview 11).

5.1.6 Marketing and sales

Marketing and sales covers three very different areas of activity: product promotion and sales; post-marketing studies and outbound logistics. The three areas have different resource requirements and the resource-management tools that are applicable to them also differ. **Work organisation methods** dominate in all three areas, but in promotion, sales and outbound logistics, a number of **business tools** are also used.

[28] For instance: the identity and role of those initiating the project, the attitudes of the project owner and the sponsor, support from the executive management of the company, the participation of external experts, the amount of time spent on training, the sense of urgency, specific targets and expectations, pilot projects in areas promising fast results, iterative deployment, „tailoring to division". I don't have sufficient room to describe these in greater detail, but the following sources provide a lot of useful information: Cooper et al. [1992], Friedman-Lyne [1999].

5.1.6.1 Increasing the efficiency of product promotion and sales

Today, pharmaceutical manufacturers do aim to improve the efficiency of *product promotion and sales*: the *relevance* of resource management is increasing continuously, and, according to my subjects, it is considered to be large today. The reason for that is that as business models based on blockbusters run out of steam, the traditionally high costs of promotion and sales cannot be supported by drugs with lower market penetration or coverage (Interview 5, Interview 8, Interview 9, Interview 11-14).

Based on the interviews I conducted, two areas are particularly important: firstly, the segmentation of products from the perspective of marketing and secondly the management of promotional expenditure. Product segmentation is a business tool and it is based on portfolio analysis (Interview 8, Interview 9, Interview 12, Interview 13). Essentially, it means that during annual planning the drug manufacturer uses certain dimensions – in particular, market potential, profitability and sales revenue – to categorise the products that it sells in individual geographic markets and uses the results of that analysis to decide the magnitude and nature of the marketing and sales resources that it would extend on the individual products. The *relevance* of product segmentation is medium relative to the entire value chain, but it is rather high in respect of the products already in the market, because it provides the basis for resource allocation.

Secondly, it seems that companies are definitely interested in managing promotional expenditure, in particular the costs of the networks of medical sales representatives, particularly because traditionally, those networks work with low efficiency, and the manufacturers can no longer afford to maintain them as revenue drops. Among the work organisation methods that are used to manage the resources allocated to the network of medical sales representatives, my subjects mentioned the outsourcing of medical sales representative work, the reduction of the frequency of visits to doctors, the introduction of alternative sales channels (“tele-visits”) and the reorganisation of networks (Interview 8, Interview 9, Interviews 11-14). Among business tools, they mentioned methodologies for measuring the efficiency of medical sales representatives (Interview 8, Interview 9, Interviews 11-14). However, my interviewees agreed that a truly efficient solution is not available as yet. They felt that the *potential* of the business tools that have been tried is medium, while their *implementability* is good and their relevance is medium. As regards

work organisation methods, their sentiment was that their potential and relevance is medium *for the time being*, but implementability is good, while they emphasised that the main factors behind the efficiency of the work of medical sales representatives are difficult to grasp using controlling tools.

5.1.6.2 Managing the costs of post-marketing surveys

Post-marketing surveys – particularly as regards the number of subjects – are similar to Phase III trials. Of the tools I listed there, structured selection of patients and data management and communication technologies are relevant here (Interview 7, Watkins [2002]). I did not obtain any information concerning the *relevance* of resource management during the research, but my impression is that it is low or medium. The paradox of implementability – namely that expected efficiency is a function of the attitudes of external stakeholders – is also applicable here.

5.1.6.3 Improving the efficiency of outbound logistics

Once more, process management plays the leading role when it comes to influencing the costs of outbound logistics. Outbound logistics constitute a mirror image of inbound logistics in the sense that the majority of the tools described there are also applicable here with some slight changes. Instead of optimising the procurement process, the objective here is the optimisation of the distribution process, while optimising the inventory levels of raw and auxiliary materials is replaced by optimising product inventory levels. In addition, the locations and tasks of distribution centres also need to be determined, with automated account management and the "streamlining" of customer services as potential actions to increase efficiency (reduce costs) also figuring into the equation. In the opinion of my interview subjects, the *potential* of such interventions is medium, but their *implementability* is relatively favourable (Interview 8, Interview 9, Interview 12), resulting in medium *relevance* overall.

5.1.7 Resource-management tools applicable to several phases of the original prescription only value chain

The resource-management tools I have described so far are all related to specific phases of the original prescription only value chain. However, those sections are organically interconnected: the development, licensing and market access processes of drugs can also be understood as a single "mega-project" which is coordinated using the tools of project management. The exploitation of the inherent opportunities of project management is a significant component of pharmaceutical industry resource management. Within the project, pricing and health-economics analyses are performed about the drug under development, and they are reviewed regularly and used to support decisions concerning the product. In theory, the efficiency of the development process can be compared with that of the companies with the best performance (*benchmarking*), the question is whether a willing cooperating partner can be found to do so.

Project management, strategic pricing and benchmarking constitute the three pillars of resource management spanning several phases of the value chain. Project management is partly a **work organisation solution** and partly a business tool, while strategic pricing and benchmarking are **business tools** only.

5.1.7.1 Project management

The task of project management is to plan the individual phases of the development, licensing and market access process of drugs, to make the required – highly varied – resources available to the project, to coordinate the expectations and information requirements of the various stakeholders, to develop the tasks and schedules of individual phases in detail, to resolve professional and cultural conflicts between the cooperating parties and to coordinate the progress of the project (Curry [2002], Rácz-Selmeczi [2001]). Project management is a resource-management tool in the sense that performing all of those tasks with aptitude may result in a tremendous reduction of costs.

Traditionally, pharmaceutical industry projects were characterised by linearity and a strict observation of sequence: any development phase could only start after the previous phase was fully completed. According to the traditional logic, even the planning of the

next phase could not begin before all the results of the previous phase were evaluated. In other words, there was no parallelism. This was related to the fact that for a long period of time, the pharmaceutical industry regarded time as a resource of unlimited availability (Interview 3, Interview 5, Interview 7, Interview 14).

The increasing pressure to innovate of the mid eighties made the large manufacturers of original drugs realise that if they allow some overlaps (parallelisms) between the subsequent phases of development, they can save significant amount of time and thereby make significant savings (Interview 8). In addition, coordination between functions can ensure that clinical and economic factors are equally taken into account. According to experience, the companies that have a separate market access team responsible for coordinating the various considerations are capable of more efficient drug development (Interview 7, Interview 14), as they are able to harmonise the clinical performance of the drug with the value story built around it. The purposeful management and organisation of the already available clinical evidence and other data that support drug development is also a task for project management (Interview 14).

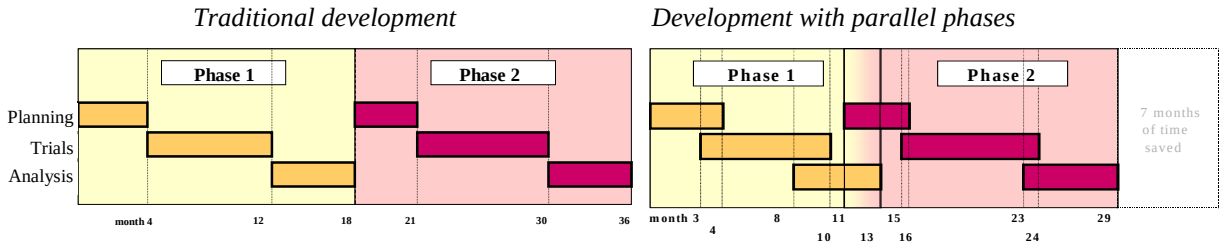


Figure 12: Opportunities in project management: the case of clinical studies (my own figure)

During drug development, overlaps that would jeopardise the safety of the development or which would infringe official regulations are not permissible (Interview 14). However, it is not a safety risk if the planning of the next phase is performed in parallel with the documentation work on the current phase, and indeed, if only paperwork is left of a particular phase, even the substantial part of the subsequent phase can be started. But it is not permissible to start a new phase when the results of the previous one are still being processed and may change. The milestone is usually the finalisation of the results.

So the task of project management is to find the critical path for the drug development project with only permissible overlaps, to distribute the resources of the project accordingly in an optimal manner and to coordinate the activities of the participants of the project. According to the subjects, its *relevance* is very high (due to its high *potential*), but the strength of traditional structures and professional groups (subcultures) within the pharmaceutical industry make project management difficult to *implement*. Nevertheless, the empirical evidence to the effect that companies adopting a project principle are more successful in drug development favours the dissemination of the new approach (Interview 14). In view of the fact that every single day by which the period to market of a drug is shortened may generate as much a million dollars in extra sales revenue, today it is the norm that project tasks that can be performed in parallel are indeed performed in parallel. With good project management, several months can be saved – which substantiates the high relevance of this tool (Watkins [2002]).

5.1.7.2 Strategic pricing

In the basic model of pricing drugs, an acceptable prince range is determined first, based on the considerations of both the market and the pharmaceutical manufacturer (Dankó-Molnár [2011], Gregson et al. [2005], Kolassa [2009]). The market approach starts with the inherent value of the drug, attempting to estimate it as accurately as possible, while the manufacturer's approach is intended to ensure that the funds invested in research and development are recovered so as to meet the expectations of the company's owners, shareholders. The market approach is used to forecast the highest price that may be charged, while the manufacturer's approach is aimed at determining the minimum price under which it is not worth marketing the new product. In the majority of cases, the so-called value-based price derived from the market approach exceeds the minimum price that the manufacturer expects, so an acceptable price range does in fact take shape. If it does not, that is a warning sign that the development of the product concerned should not be continued due to economic reasons.

The real question is the determination of the value-based price. The true value of a drug is clearly not the quantified value of the chemicals that compose it, and neither is it the value of the development work invested, divided by the amount produced. The value that pricing aims to determine has a lot more to do with the drug's competitive

advantage, i.e. its factors overlap with the factors that generate competitive advantage. The value of a new drug is usually derived from the added therapeutic value, the proven competitive advantage over other therapies, and the manufacturer's marketing ability to communicate those advantages towards customers.

The value is relative, so it is determined in relation to other, already available drugs, surgical interventions or other palliative therapies. The price of the alternative medical technology will be the reference value for the drug; it is relative to that that the competitive advantages need to be determined and their so-called differential value needs to be quantified. The final differential value will be the sum total of positive and negative components: certain properties of the new drug will increase, while others will decrease its value relative to the reference value.

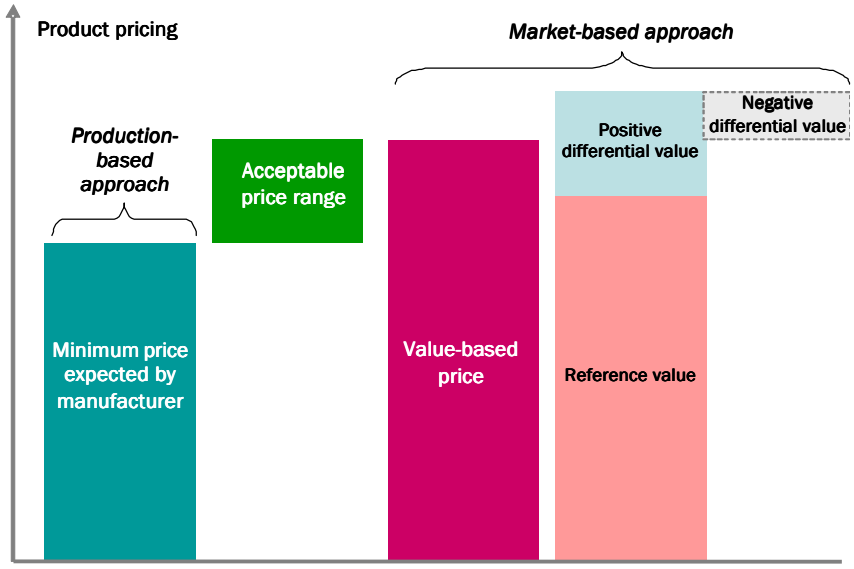


Figure 13: Pricing model for original pharmaceuticals
(Source: based on Gregson et al. [2005], with some modifications)

In the first instance, determining the differential value is a task for specialists in health economics. In theory, they are seeking the value that the new drug generates for society in terms of an increase in health gained, therapeutic costs avoided, reductions in environmental loads and increased productivity. In order to determine that value, they look at the number of patients with the indication of the drug, the incidence of new cases and the way that is going to change in the future as well as the costs and results of the standard and the newly developed therapies. They use health economics models to determine all those, and they attempt to conceive of the value as the unit total of health

improvement and cost reduction (per unit of active ingredient) for society as a whole. Naturally, they develop a number of scenarios that differ in the target indications and relevant parts of the population – these scenarios are going to be of critical importance for the development of the drug as a whole, because to a large extent they will determine the first indication for which the drug will finally be marketed.

In contrast, the determination of the minimum price expected by the manufacturer is a complex task of net present value calculation. A 10 to 12% expected profit is usually taken into account for calculating that price, which is an expression of the higher risk of pharmaceutical industry investments. Subsequently, the minimum price expected by the manufacturer is the price at which, calculating revenues, the net present value of the drug development project is at least zero, or the minimum amount expected by shareholders. When determining the minimum price expected by the manufacturer, the assumptions made about the rate of growth of the drug's market share are of key importance: if the market is slow to accept the product, there will be less truly profitable years left before loss of exclusivity.

Drug pricing is not a one-off activity but a process taking several years. The organisational units working on drug discovery, marketing, clinical development, risk management and market access all participate in it, the last one of those also including the specialists that create the health economics models. The above process is repeated in several iterations, with accuracy and focus increasing in each iteration (Interview 2). It is exceptionally important that the results of these analyses feed back into the drug development process at several points: the earliest feedback point occurs when the market access unit has marketing and the specialists performing clinical development validate the first pricing model. After that, mutual feedback becomes continuous: as the ideas concerning the target price take shape, indications or patient groups are specified with greater accuracy, and vice versa. In addition, the pricing strategy also has an important role to play in defining the clinical targets used in Phase III trials: of the pharmacologically possible and available targets, those should be chosen that are best able to justify the targeted price.

According to the results of my research, the *potential* and the *relevance* of strategic pricing are both very high, which is explained primarily by the fact that its results have a

fundamental feedback effect on drug development: one major case of that is the modification of indications, while the other is the determination of the sequence of market access, while the third possibility is actually stopping the development project (Interview 2, Interview 3, Interview 5, Interview 7, Interview 8, Interview 11-14). Strategic pricing requires the cooperation of the market access division, the health economics team, marketing and clinical development, so is *implementability* is subject to the same considerations as that of project management. Today, it is generally being used by all large pharmaceutical companies.

5.1.7.3 Benchmarking

Benchmarking is the comparison of the company's performance with the performance of the best companies in comparable areas or using comparable processes, with the purpose of making the operation of the company more efficient by using the experiences of the benchmark firms (Camp [1998]). Benchmarking is actually an initiative of adopting the best practice (usually the industry best practice).

According to the pharmaceutical industry specialists I have interviewed, classical, "trust-based" benchmarking is not viable because in the current climate of sharp market competition, companies are treating all their internal information confidentially: they believe that the benefits of learning from others are not worth taking the risk of their partners tapping into their know-how, the source of their competitive advantages. This fear is reinforced by the fact that pharmaceutical companies are proceeding along parallel tracks: they think in very similar ways and they hardly have any internal information that they could share with others without jeopardising their own security (Interview 5, Interview 7, Interview 14, Woodcock [1997]).

Although pharmaceutical industry benchmarking may offer significant opportunities for cost reductions, it seems it is not workable in the original pharmaceuticals industry at this time. Forums for it could be provided by industry advocacy federations, but they are actually only used for advocacy and they are themselves also regulatory authorities that have some level of access to all projects that reach the clinical phase. However, in order to turn those forums into forums of genuine information exchange, the industry's attitudes and competitive conditions would both have to undergo significant changes.

5.2 Resource management in the generic prescription-only value chain

The characteristics of resource management at generic prescription-only (GRX) pharmaceutical companies appear to be different to those of the manufacturers of original drugs. I shall review the possibilities along the specific generic value chain, with the provision that wherever the tools available are partly or wholly identical to those used by original manufacturers, I shall not detail them again. Instead, I shall include references to the appropriate subsections of *Section 5.1*.

5.2.1 Compound development

Generic compound development consists of finding, formulating and establishing economical production pathways (production technology) for compounds that match the profile of the company, which are technologically "duplicable" and whose patents expire at the required time.

The literature has little to offer about the resource-management techniques available for *patent research*, and my research has also yielded only limited results about this issue. So I only draw attention to a single important procedure: the structuring of patent research, which is a work organisation solution. In view of the fact that the majority of generic companies have specialised in well-defined therapeutic areas, the basis for patent research is a knowledge of that area and access to physical and "non-physical" databases (the latter in people's heads). Once the competitors, the available technologies and pharmacological characteristics are known, patent research can be structured quite well, and that results in a reduction of research costs. On the other hand, the companies examine the patents they find interesting from a great number of technological and economic perspectives, aiming to screen out compounds that do not offer market success as soon as possible. Some patents (compounds) can be screened using simple qualitative analyses, so the resource-intensive quantitative analyses only need to be performed for compounds whose production is actually contemplated seriously (Interview 6, Interview 10).

The synthesis pathways of the selected molecules are largely patented by the original manufacturers, so it is difficult to find a production technology that is not encumbered by any patents. Therefore process

patents are researched together with product patents, and they usually eliminate molecules that are rendered unviable by process patents in the qualitative phase of the research. This requires the company to have a good pharmacologist with expertise in all the details of his field of specialisation, who can review the existing process patents and forecast whether there is a possibility of developing alternative synthesis pathways.

If the company judges the industrial synthesis of a compound to be economically and technologically feasible, it produces and formulates the compound, and it also attempts to develop an innovative *production technology* for it. The latter is a process chemistry task and as such, the findings of *Section 5.1.2.3* are applicable, with the provision that of the possible production pathways, only those not under patent protection can be considered. The most efficient one of those needs to be selected. The generic manufacturers often do not deal with process chemistry themselves but outsource it to the chemical industry company that they wish to purchase the active ingredient from later. The outsourcing can save costs, as the suppliers have greater experience in the field of producing active compounds on an industrial scale and they also work with larger volumes. As a result, their prices are below the cost of in-house production (Interview 4, Interview 6, McCoy [2002]).

According to the results of my interviews, the resource-management tools used in the relatively less costly phase of compound synthesis are not particularly innovative, or they do not contain any solutions that are novel relative to those used by the manufacturers of original drugs. Structuring patent research is important when selecting the molecule, while during reproduction, thinking in terms of process chemistry *or* outsourcing the development of the production technology are the important tools. Significant cost savings can be achieved primarily by choosing the right process chemistry, so that seems to have the highest relevance. The *potential* and *relevance* of structuring patent research are both medium. The relevance of outsourcing is higher, and in actual fact, an increasing number of generic drug manufacturers are buying the active ingredients required for their products in the market. *Implementability* is subject to the same conditions that I described for original drug manufacturers – i.e. the attitudes of various members of the organisations towards individual resource-management initiatives is primarily not a function of their relevance but the organisational changes that they entail (Interview 6, Interview 13).

5.2.2 Preclinical and clinical trials, licensing

The development of generic drugs usually does not require preclinical and clinical trials, it is sufficient to provide evidence for the human bioequivalence of the drug. When more detailed tests are necessary, they are usually still not comparable in extent to the trials of original drugs (Interview 2, Interview 6, Interview 10). On the other hand, bioequivalence trials are an organic part of the development of any generic drug. The authorities do not require identity with the original drug, but they do evaluate the results of those tests stringently. As a result, it is in the interest of generic pharmaceutical firms to cooperate intensively with the authorities so as to ensure that the company does not happen to run out of the time available until "day zero" (the expiry date of the patent). When, in the case of non-bioequivalent generics or biosimilar drugs, clinical trials are required, my interview subjects mentioned proactive cooperation with the regulatory authorities, the structured selection of patients and the careful selection of trial locations as relevant among the techniques used during original development (Interview 6, Interview 10)[29]. Those are all work organisation solutions.

The limited nature of the trials performed on generic drugs also constrains the *potential* of resource management, but it should not be underestimated, because in the competition between generics, those reaching the market first can achieve a long-term competitive advantage (Interview 10). Once again, *implementability* is largely a function of the attitudes of the cooperating partners – particularly the regulatory authority.

According to my interview subjects, the trials and licensing – and the associated resource-management techniques – cannot be separated from each other: there is no strict boundary between them in terms of time or in terms of attitude (Interview 6). During the licensing phase, proactive cooperation with the regulatory authorities still has the leading role. The *relevance* of resource management is constrained by the same factor as in the case of bioequivalence trials: the expiry of the original patent (the exclusive right to market the compound) is an objective limit on market access, but any delays relative to that deadline should be avoided. In view of that, the experts I questioned believed that *potential* was medium-level. Once again, *implementability* is influenced the most by the regulatory authority.

5.2.3 Production

5.2.3.1 General considerations

Based on the results of *Section 5.1*, the focus of resource management by the original drug manufacturers is on maximising the efficiency of the development and licensing process. They are able to influence the production phase using techniques of medium relevance, primarily due to the limited opportunities to achieve strategic advantages. My research indicates that in the case of the manufacturers of generics, the balance is the opposite: in their case, the costs of the development and licensing process are "sufferable", but the products encounter strong competition of price after they are introduced to the market. As a result of those two factors, the importance of techniques associated with the production and sales phases is greatly increased (Interview 3, Interview 6). The techniques involved are largely **work organisation solutions**, supported by some **business tools**. Scientific and technological solutions do not play a role in those phases.

The generic drug manufacturers that I interviewed consider the establishment of a process background for efficient production to be their prime strategic task (Interview 6). Their *process efficiency* and their flexibility are the major sources of their competitive advantages. Contrary to the strongly functional approach that characterises original manufacturers, the leaner generic companies with less employees are characterised by much a much stronger focus on thinking in terms of processes. In their supplier relationships, they aim for flexibility and minimising their costs as well as long-term partnerships. The resource-management techniques that they use to support the production phase are also characterised by a process-centred approach and a commitment to flexibility, accompanied by robust capacity management. Generic pharmaceutical companies outsource everything to external partners that they cannot do economically internally (Interview 6, Interview 10).

The *process approach* permeates all areas of production and outbound logistics. While observing the requirements of Good Manufacturing Practice (GMP), the emphasis is on

[29] A more detailed description of those techniques is provided in *Section 5.1.3*.

increasing the efficiency of procurement and support activities and on the perfection of the product flow process viewed from a *global perspective*. The latter means that generic companies take the core of production, i.e. the product manufacturing process that is difficult to develop as a given, and attempt to control all the partial processes open to adjustment so as to ensure that they produce the required output by the exact deadline required (Interview 3).

Flexibility is the ability to adapt quickly. Generic pharmaceutical manufacturers need to be flexible both as customers and as vendors (Interview 3, Interview 10). *Customer side* flexibility means that generic companies always choose the supplier offering the best mix of reliability, low prices, speed and adaptability. They aim to form long-term relationships, but they also keep an eye on maintaining a continuous price advantage. *Vendor* flexibility involves the continuous monitoring of geographic and product-based partial markets and adjusting logistical capabilities accordingly.

Capacity management – largely taking the form of outsourcing – is the technique that provides the main evidence for the intention to streamline the company. True generic pharma companies outsource all activities that would require a costly infrastructure to perform in-house to external partners: they purchase the active ingredients from suppliers, or they outsource the packaging of their formulated preparations. The generic pharma companies themselves largely provide the licensing and sales capacities, while the physical product itself is often produced by "contract manufacturers" (Interview 3, Interview 6).

In the case of generic manufacturers, implementability is improved by the fact that, due to market pressure and their leaner organisations, the efficiency-focussed attitude is entrenched deeper in their operations than in the case of original manufacturers. They are better able to tolerate uncertainty as well, so the organisational shocks resulting from resource management are not so pronounced in their case (Interview 6, Interview 10).

5.2.3.2 Endeavours to control the costs of the partial processes of production

In the opinion of the specialists I interviewed, the key factor of *procurement* is that the active ingredients and auxiliary materials that compose medical preparations must be

available just in time, in just the required quantities. In the final analysis, this entails the purposeful reduction of inventory levels and the associated direct and indirect costs (salaries, costs of machinery and equipment, capacity costs, overheads, administrative costs, etc.). Several conditions must be met at the same time in order not to jeopardise the security of ideally *just-in-time* production: a sophisticated production management system needs to be in place that is able to complete procurement operations quickly, and which is connected, if possible, to the corresponding systems of the suppliers. On the other hand, there need to be quality norms and criteria for selecting suppliers that are suitable for assessing potential partners from anywhere in the world quickly and decisively when needed. Finally, by modernising warehousing and transportation methods, inbound logistics must be made capable of performing its tasks in a fast and exact manner (Interview 3). These techniques are partly work organisation solutions and partly business tools (supplier selection criteria and customer audits). The interviewees claimed that they had medium or high *relevance*, while they assessed their *implementability* (with the exception of the just-in-time system) as good or variable. Overall, they felt that their *relevance* was also medium or high.

Production in the narrow sense is subject to the requirements of GMP, but still, resource-management solutions play a pronounced role. Production engineering criteria are the critical ones when determining the optimal batch size, so, along with the direct costs of production, the indirect costs of logistics are also quantified (Interview 3). Production capacities need to be organised so as to allow a single plant to produce several, technologically similar products. As a result, it becomes easier to comply with GMP, flexibility is gained, and the sequence of series becomes more programmable. The production process can also be improved by setting the control points in a rational manner, in accordance with the criteria of cost prevention. There is no general recipe for the setting of control points – each company has to develop this for itself (Interview 10). Outsourcing is also a particularly important resource-management technique of the production phase. The outsourcing of the production of active ingredients has become a general practice: the majority of generic pharma companies purchase the active ingredients for their drugs from the precision chemistry industry, and in most cases they only do the formulation themselves. The active ingredients are usually supplied by the companies that were previously commissioned to develop the process chemistry, or who were the suppliers of the original active ingredient as well (Interview 6). In view of all

that, the *potential* of the solutions in use is high or medium, *implementability* is largely good or variable, while *relevance* is medium or high.

In *packaging*, technological development offered cost savings for a long time. Thanks to the increasing modernisation of packaging lines and materials, the packaging of final products has become smaller, lighter, more environment-friendly and, last but not least, cheaper as well (Interview 3, Rácz-Selmeczi [2001]). More recently, there appears to be a trend of outsourcing packaging to logistics partners with more sophisticated logistical capabilities. *Potential* and *relevance* are both minor or medium. (Interview 4).

The optimisation of *processes that support production* is an objective for all generic manufacturers. The proliferation of activities that do not generate value directly may result in a high level of general costs. The specialists interviewed reported the use of multi-level coverage calculation and process-based costing techniques (Interview 3, Interview 6, Interview 10). In addition, a number of publicly available case studies also describe how generic pharma companies have attempted to map their support processes and to divest unused resources through process cost management (see e.g. Taylor [2000], Kaplan-Weiss-Desheh [1997]). These methods have medium *potential* and *relevance*.

5.2.4 Marketing and sales

In the area of *product management* and *product promotion*, the generic companies seem to be going through the same learning cycle as original companies (Interview 3, Interview 10). While previously – in the drug markets using brand-name based ordering – the generic companies did not pay much attention to the efficiency of sales and marketing, either, today, this is becoming increasingly significant. Among **business tools**, my interviewees emphasised the role of multi-level coverage calculation schemes and calculation of return, while among **work organisation solutions**, they noted the streamlining of medical sales representative networks, the primary use of contract medical sales representative services and alternative sales channels. This implies that the *relevance* of resource management is gradually increasing in this area, but, according to my interview subjects, it remains at a medium level for the time being. The interviewees mentioned the problem of how far doctors are willing to accept sales techniques that are

company-independent or do not involve personal contact in the (Interview 3, Interview 10) as specific to strongly marketing-driven national markets.

The process approach and the endeavour to achieve flexibility have a strong presence in *outbound logistics* as well – primarily in the form of **work organisation solutions**. Generic manufacturers organise these processes using the same principles they use for procurement. Their primary objectives are to minimise their inventory levels, to locate their distribution centres optimally for their markets and to achieve the highest possible flexibility of supply as a result (Interview 3, Interview 6). They also aim to render liaison with customers – including the performance of business transactions – as smooth as possible.

In the phase of outbound logistics, the *relevance* of resource management is medium or high according to the experts I questioned, with good implementability, but it is difficult to analyse separately from production due to the integration of processes.

5.2.5 Resource-management techniques that cover several phases of the generic prescription only value chain

The techniques I described for original pharma companies are also available to generic firms, sometimes even with better implementability (Interview 3, Interview 6, Interview 10). The explanation for that is that the lifecycle (value chain) of generic drugs is short relative to originals, and the events along their value chain are more amenable to planning, so the techniques covering several phases have more exact numerical data to work on.

Due to the relative simplicity of generic development, project management is less relevant than for original companies. Though it is not a revelation, it is certainly true that the importance of project management is proportional to the number, complexity and coordination requirements of the tasks to be performed. The interviewees felt that its *potential* and *relevance* were both very high.

Strategic pricing and, as a part of that, health economics analyses are used by generic companies as well, though, according to the specialists I interviewed, their *relevance* is

lower than in the case of original manufacturers, due to pricing constraints. It is easier for them to use these techniques because they can perform the analyses with greater accuracy right from the outset. Some generic companies support the decision to launch development by performing a life-cycle analysis (Interview 3, Interview 10). The advantage of such an analysis is that it is able to characterise the market, the entry costs as well as longer-term prospects based on much more accurate data.

The role of *benchmarking* is minor in the case of generic companies as well (Interview 6). When building databases, they primarily use publicly available data and they perform their analyses alone.

6. Summary conclusions

6.1 Results and limitations

In *Chapter 5* of the doctoral thesis I attempted to explore the characteristics of pharmaceutical industry efficiency improvement (resource management) in the original prescription only and the generic prescription only strategic models based on in-depth interviews conducted with 14 pharmaceutical specialists working in various areas. In my view, the added value of the research I have performed is that it examines the workings of the pharmaceutical industry from a management-science perspective that, as far as I know, has not been used for this purpose in Hungary before. Secondly, I feel that I have managed to achieve an almost comprehensive view of the solutions used in pharmaceutical resource management to a level of detail that is appropriate for an analysis intended to open a new avenue of research. The approach of dividing the tools of improving efficiency into scientific and technological solutions, work organisation solutions and business tools has proven expedient for the research and rendered my work easier. It is probable that an approach focussing exclusively on business tools would have resulted in distorted and non-representative results, which I was able to avoid by adopting the above wider perspective,.

I believe it is a further result of the research that it may serve as the foundation for further research (see *Section 6.5*), which would be more difficult to conduct without the information that I gathered. It is also an advantage that, based on my impressions gathered during the in-depth interviews, there is increasing interest in the industry in understanding and testing the methodologies available in the field of resource management, and my dissertation – due to its comprehensive overview character – can serve as a guide for that endeavour. I feel it is a further result that the approach of the thesis can also be used in other industries characterised by long-term returns and the fundamental influence of decision made in the initial phase of projects on future scope of action (path dependence) and/or a high degree of regulation.

Naturally, the research I performed also has limitations. On the one hand, when I processed the results, I had ample opportunity to verify the old adage that when opening a new direction of research, the trade-off between producing a comprehensive view and going into sufficient detail needs to be taken very seriously indeed. The fact that in my dissertation I reviewed the entire value chains of two pharmaceutical strategic models made it impossible to go into the level of detail concerning individual techniques that they deserve. Under that constraint I chose the option of presenting those techniques in greater detail that may constitute novelties for economists (or "managers"), while I included less detail or even provided no explanation at all of methodologies that do not need much explanation in my own profession (e.g. controlling-type tools).

Furthermore, it is certain that the terminology I used will have to be refined further in the future. In my dissertation – as I explained in *Chapter 1* – I purposefully avoided conceptual argumentation, but it is clear that Chapter 2 only begins to clarify the concept of resource management, and that the specialist terminology I have used needs to be matured in several iterations. It is conceivable that the term "efficiency management" would be a better match than "resource management" for the items I discussed in my dissertation, but that term is by no means entrenched in Hungarian specialist terminology.

I believe it is a further limitation that I was unable to fill out the analytical framework defined in *Section 4.1* completely, due to the methodology based on on-depth interviews and the extent of the research. There are some areas (phases of the value chains) in which I was able to get a grip on and illustrate both potential and implementability, but in other areas I was not able to do this, so I could only achieve an approximate assessment of relevance. It is probable that I would have achieved more consistent and "homogeneous" results if I had studied only a single specific value chain – my more comprehensive, horizontal approach had the disadvantage that I was only able to document the factors behind potential in detail to a limited extent.

Despite all those limitations I hope that my dissertation contributes to an improved understanding of the workings of the pharmaceutical industry from a novel, management science perspective. Below, I shall present my main conclusions about the original prescription only and the generic prescription only value chains, followed by an

examination of the extent to which I was able to confirm or reject the research hypotheses that I formulated.

6.2 Resource management in the original prescription only (ORX) strategic model – general conclusions

I shall present my summary conclusions in relation to the pharmaceutical manufacturers of original prescription only (ORX) drugs first. If we consider the development, market access and sales process as a value chain, the value chain of those companies is very long, covering up to two decades. The value chain consists of several phases with radically different characteristics, and efficiency is increased by different sets of resource-management tools in the various phases. The range of resource-management techniques is extremely wide: it includes technological and scientific, work organisation and business tools.

The competition between original pharmaceutical manufacturers takes place in the field of innovation. Their profit is derived from innovation – in Schumpeter's terms, new technological processes and, most of all, product innovation (Antalóczy [1997], Roberts [1999]). The most important source of competitive advantage for them is how fast they are able to place a new product in the market. The sooner the preparation reaches patients, the more time they have left of the period of patent protection (exclusive market access) to generate revenue, so the more profit they are able to make. That profit provides the foundation for developing subsequent products; in that sense, continuous innovation is its own precondition. Despite the fact that the company's innovate in competition with each other, the greatest enemy is *time* itself. Original manufacturers must defeat time – and the outcome of that battle also decides the outcome of the fight against each other. As I have already mentioned, it is estimated that each day saved in the development process may result in additional revenue of up to one million dollars (Sweeny [2002]), and the reverse is also true: delays in development can result in tremendous losses of revenue not to mention the additional costs of development and licensing.

So, in the original prescription only model, the main tasks of resource management are to accelerate the development process, to prevent avoidable costs and to eliminate

superfluous activities. As a result, the most important resource-management tools are those covering several phases, i.e. the longitudinal ones: those tools – as they save time and reduce risks – are the most important of the solutions identified in *Chapter 5*.

So the essence of efficiency improvement (resource management) conducted by original pharmaceutical manufacturers is the prevention of costs and risks, even at the cost of greater up-front investment. All activities, phases of work, processes and assignments of tasks should be eliminated whose later time requirement does or may result in additional costs. This is rarely possible to do using business tools, so in the phases of the value chain prior to the marketing of the drug, scientific and technological solutions and work organisation solutions appear to be more important. Due to the nature of the work tasks to be performed, the business tools widely documented in the management literature (e.g. controlling tools) have limited relevance, as in the original pharmaceutical industry most of those are simply not worth using because they are not capable of producing true competitive advantage. The medical and official requirements applicable to medicines, the biochemical properties of drug molecules, the characteristics of the technology of organic chemistry and the areas with high administrative burdens – e.g. quality management and environmental protection – are all unavoidable, which do not favour the use and acceptance of classical process development or the "textbook" varieties of costing and systems of indicators. Business tools in themselves are therefore unlikely to achieve substantial improvements of efficiency in the original pharmaceutical industry. As a general rule, their significance increases after the drug is placed in the market, when they serve as the basis for portfolio decision, *make-or-buy* decisions and capacity decisions.

However, there are some exceptions: of the methodologies that are taught (among other places) at university courses in economics, project management and other methodologies that can be used within the framework of strategic pricing (e.g. net present value calculation) have markedly high relevance, but in practice those are also extended using industry-specific characteristics which, according to the traditional functional classification, belong among marketing tools, public relations tools and IT solutions.

The implication is that resource management in original pharmaceutics is an interdisciplinary activity. It covers several aspects of clinical pharmacology,

pharmacological technology, project management, marketing, public relations, controlling and information technologies. The question is, what is the significance of such a diverse activity relative to other strategic activities. Based on my in-depth interviews with pharmaceutical industry specialists I have formed the impression that for them, resource management is the totality of efforts made to increase efficiency and reduce risk. In that sense, they understand the role of resource management clearly, but many of my interviewees added that its significance does not match that of influencing the market in a proactive manner or continually renewing the product portfolio.

Original pharmaceutical companies aim to develop their processes and to develop their internal efficiency, too, but they do so in a much less spectacular fashion than those in other industries, as taking such measures only result in competitive advantages for them if they have an innovative and market-ready basic product. It may also play a role that original companies are large, inflexible and tend to avoid risks, while they are permeated by everyday rituals of operation (Desjardins [1997]). In their case, success is the result of innovation, innovation requires capital strength and capital strength is indirectly a function of size. But there is a trade-off between size and flexibility: for a pharmaceutical company to be large and stable in the long-term, it needs standardised operating processes, and standardised processes reduce flexibility (Allen [1997]). It is no accident that original pharmaceutical manufacturers outsource the research and development tasks requiring flexibility and the taking of higher risks – their sluggishness and their internal coordination mechanisms do not bode well for the success of those activities. Regulatory factors such as the strict GMP regulations also contribute to that effect.

In summary, based on my research:

- **In the original prescription only strategic model, the significance of resource management using business tools is low, with the exception of project management and the methodologies used for strategic pricing.**
- **However, scientific and technological solutions and work organisation solutions do play an important role in improving organisational efficiency, although their significance in promoting business success still remains below tools such as continuous product innovation (*pipeline*) and the proactive influencing of the market.**
- **In the original strategic model, the focus of increasing efficiency is on preventing costs and risks in a forward-looking and interdisciplinary manner.**

The resource management solutions used in the original prescription only model are shown in *Table 5*, which was compiled as a summary of the results of my research. The table contains all the tools listed in *Chapter 5* along with their potential, implementability and perceived relevance as reported by the interview subjects.

Value chain phase	Category	Type	Solution	Potential	Implementability	Perceived relevance
Discovery and synthesis	Longitudinal tools	Scientific and technological solutions	Combinatorial chemistry and screening methods	Very great	Medium	Very great
		Work organisation methods	Acceleration of work process	Minor	Medium	Minor
			More efficient work organisation			
			Better raw material management			
	Cross-section tools	Computer assisted drug research (scientific and technological solution)	Structure-driven drug design	Great	Not possible to assess in general	Great
			Targeted design			
			Virtual screening			
		Pharmacogenomics (scientific and technological solution)		Medium	Not possible to assess in general	Medium
	Reduction of capacity costs	Rationalisation (work organisation solution)	Across-the-board rationalisation	Variable / Great	Medium	Medium / Great
			Differentiated rationalisation	Variable / Great	Difficult	Medium / Great
		Outsourcing (work organisation solution)	Full outsourcing	Medium / Great	Uncertain	Medium / Great
			Partial outsourcing			
Preclinical trials	Frontloading	Scientific and technological solutions	In silico testing	Very great	Difficult	Great
			Trial design			
			Parallel trials			
			Acceleration of carcinogenicity trials			
		Work organisation methods	Acceleration of work process	Medium	Medium	Medium

Value chain phase	Category	Type	Solution	Potential	Implementability	Perceived relevance
			More efficient work organisation			
			Better raw materials management			
	Outsourcing preclinical trials (work organisation solution)		Full outsourcing	Medium	Not possible to assess in general	Medium
			Partial outsourcing			
	Prevention going beyond preclinical phase	Process chemistry (scientific and technological solution)		Great	Not possible to assess in general	Great
Clinical trials	Close cooperation with regulatory authorities (work organisation solution)			Great	Partly depends on external stakeholders, partly requires a change of attitudes, hence difficult	Great
	Structured selection of patients (work organisation solution, with some scientific and technological elements)			Very great		Very great
	Careful selection of trial configuration and locations (work organisation solution)			Very great		Very great
	Phase 0 and *proof of concept* trials (work organisation solution, with some scientific and technological elements)			Very great		Very great
	Limited registration			Very great		Very great
	Use of data management and communication technology (work organisation solution)			Great	Variable	Great
	Strategic pricing (business tool)			*See tools covering several phases of the value chain*		
	Project management (business tool)			*See tools covering several phases of the value chain*		
Licensing and registration	Consultations with regulatory and financing authorities (work organisation solution)			Medium	Depends on external stakeholders	Medium
Production	Optimisation of activities associated with procurement and inbound logistics	Optimisation of procurement process (work organisation solution)		Medium	Good	Medium
		Maintaining high quality of supply (work organisation solution)				
		Achieving optimal stock levels (work organisation solution)				
	Optimisation of production capacities	Outsourcing	Outsourcing active ingredient production (work organisation solution)	Medium	Generally good	Medium
			Outsourcing packaging (work organisation solution)	Medium	Good	Medium
		In-plant rationalisation (work organisation solution)		Minor	Medium / Difficult	Minor / medium
		Concentration of production capacities (work organisation solution)		Minor	Medium / Difficult	Minor / medium
	Streamlining of support infrastructure	Process management (business tool)		Medium	Variable	Medium
	Other business tools			Medium	Variable	Medium
Marketing and sales	Increasing the efficiency of product promotion and sales	Product segmentation(business tool)		Medium	Good	Medium
		Reducing promotional costs (work organisation solution)	Outsourcing the work of medical sales reps	Medium for the time being	Variable	Medium for the time being
			Reorganisation of medical sales rep network			
			Alternative sales channels			
	Controlling the costs of postmarketing tests	Structured selection of patients (work organisation solution, with scientific and technological elements)		[Minor or medium]	Depends on external stakeholders	[Minor or medium]
		Data management and communication technologies			Variable	
	Improving the efficiency of outbound logistics	Optimisation of the distribution process (work organisation solution)		Medium	Good	Medium
		Optimisation of product inventories (work organisation solution)				
		Management of distribution centres (work organisation solution)				

Value chain phase	Category	Type	Solution	Potential	Implementability	Perceived relevance
		Streamlining account management and customer relations (work organisation solution)				
Tools covering several phases of the value chain	Project management (business tool)			Very great	Variable	Very great
	Strategic pricing (business tool)			Very great	Variable	Very great
	Benchmarking (business tool)			Minor	Poor	Minor

Table 5: Overview of the resource-management solutions used in the value chain of original prescription-only drugs

6.3 Resource management in the generic prescription only (GRX) strategic model – general conclusions

Various resource-management tools correspond to the various phases of the value chain in the generic prescription only strategic model as well. The value chain has fewer phases than that of originators, largely due to the lack of a clinical development phase and the relative simplicity of licensing. As a result, the tools used for improving efficiency also exhibit less variety.

Although marketing-driven product markets are quite common, price is the definitive factor in the competition between generic manufacturers. Their competition against time is less crucial, although they do have to take the expiry of the exclusive market access of the originators in mind. As a result, with generic manufacturers the performance of production, marketing and sales is at least as important if not more important than that of compound development and licensing.

In the development and licensing phases, generic manufacturers are also characterised by cost prevention, but its significance is lower relative to the original prescription only strategic model. On the other hand, as they operate in a competitive rather than a monopoly market, they are under much greater pressure to operate their production and sales in an efficient manner. Price competition forces them to exploit all the reserve capacities in the operation of their organisations and to be flexible. As a result, the operation of generic firms in the period after drugs are placed in the market appears to be much tighter and “leaner”. Increasing efficiency is a continuous endeavour that is a part of everyday work, whose focus is not so much on the longitudinal tools of influencing costs but on optimising operating processes.

In the interest of maintaining cost-effectiveness and flexibility, the companies using the generic prescription only model tend to use the solutions for efficiency improvement that are to be found in the pages of management textbooks to a greater extent. Work organisation methods and business tools are more suitable for the optimisation of operating processes. Accordingly, the resource management of the generic prescription only model is also interdisciplinary in character, but there is an observable shift of emphasis towards the use of business tools. According to the results of the interviews, work organisation solutions and business tools are in general use, and the gap between the significance of scientific and technological solutions and other methods is not as great as in the original prescription only model.

Presumably, the importance of achieving organisational efficiency is proportional to the intensity of price competition in the market of active ingredients that are no longer under patent protection. In markets where brand-based drug ordering is dominant, doctors think in terms of brand names rather than active ingredients, and marketing, as a factor of success, may be more important than improving efficiency. In those markets, however, where competition of substitutable drugs is really efficient, and/or where the financing authority uses administrative means to enforce drug prices that are near the marginal cost, the role of resource management increases exponentially.

Actually, according to the specialists I have questioned, the duality of increasing efficiency and influencing the markets is characteristic of the generic prescription only strategic model as well: while functional resource management is vitally important, it is not worth much if marketing work and product portfolio management are weak. So in this respect there is no striking difference between original and generic pharmaceutical companies.

In summary, based on my research:

- **In the price-driven generic prescription only strategic model, resource management is strongly focussed on the efficiency and flexibility of operating processes.**
- **As daily operating processes are in the focus of attention, the significance of work organisation solutions and in particular that of business tools is greater than in the original prescription only strategic model.**
- **Appropriate resource management is a necessary, but not sufficient condition of business success in the generic prescription only strategic model. It does appear to be a lot more important than in the case of original pharmaceutical manufacturers, which operate in monopoly markets.**

Table 6 below presents the tools of resource management used in the generic prescription only business model in a manner similar to the way *Table 5* did so for the original prescription only model:

Value chain phase	Category / type	Solution	Potential	Implementability	Perceived relevance
Compound development	Patent research management	Structuring of patent research (work organisation solution)	Medium	Good	Medium
	Production technology management	Process chemistry (scientific and technological solution)	Medium / Great	Variable	Medium
		Outsourcing of production technology (work organisation solution)	Great	Variable	Medium / Great
Preclinical and clinical trials, licensing	Close cooperation with the regulatory authorities (work organisation solution)		Medium	Depends on external stakeholders	Medium
	Structured selection of patients (work organisation solution)				
	Selection of trial locations (work organisation solution)				
Production	Procurement management	Just-in-time production management (work organisation solution)	Great	Difficult	Great
		Quality norms and supplier selection criteria (business tool)	Great	Good / variable	Great
		Customer audits (business tool)	Medium / Great	Good / variable	Medium / Great
		Modernisation of warehousing and transportation (work organisation solution)	Medium	Variable	Medium
	Production cost management	Determination of optimal batch size (work organisation solution with scientific and technological elements)	Great	Good / variable	Great
		Homogeneous plants (work organisation solution with scientific and technological elements)	Great	Medium / Difficult	Great
		Optimal selection of control points (work organisation solution)	Medium	Good	Medium
		Outsourcing (work organisation solution)	Very great	Variable	Great
	Optimisation of packaging	Optimisation of packaging (scientific and technological solution)	Minor	Good	Minor / Medium
		Outsourcing (work organisation solution)	Medium	Variable	Medium
	Optimisation of supporting processes	Process management (work organisation solution supported by business tools)	Medium	Variable	Medium

Value chain phase	Category / type	Solution	Potential	Implementability	Perceived relevance
Marketing and sales	Product management	Coverage and returns calculation methodologies (business tools)	Medium	Good	Medium
	Product promotion management	Streamlining of medical sales rep networks (work organisation solution)	Medium / great	Variable	Medium
		Outsourcing of doctor visits, "contract reps" (work organisation solution)	Medium / great	Variable	Medium / great
		Alternative sales channels (work organisation solution)	Medium / great	Variable	Medium / great
	Improving the efficiency of outbound logistics	Optimisation of the distribution process (work organisation solution)	Medium / great	Good	Medium / great
		Optimisation of the stock level of finished product (work organisation solution)	Medium / great	Good	Medium / great
		Management of distribution centres (work organisation solution)	Medium / great	Good	Medium / great
Tools covering several phases of the value chain	Project management (business tool)		Very great	Variable	Very great
	Strategic pricing (business tool)		Nagy	Variable	Great
	Benchmarking (business tool)		Minor	Poor	Minor

Table 6: Overview of the resource-management solutions used in the value chain of generic prescription-only drugs

6.4 Conclusions concerning the hypotheses

In summary, some of the hypotheses I formulated for my research were fully supported by the results of the qualitative study, while some of them were only partially validated and hence required amendment. In my opinion, none of the hypotheses have proven completely false. Reviewing them one by one:

- Hypothesis H1 – "*In the preclinical phase of the value chains, scientific and technological solutions have the greatest perceived relevance, with work organisation tools in second place and business tools coming last*" – seems to have been substantiated in both of the strategic models I examined, although to differing degrees and in particular with different robustness:
    - The empirical results indicate that in the original prescription only (ORX) model, in the preclinical phase the most relevant techniques are the scientific and technological solutions of combinatorial chemistry (including screening methods), computer assisted drug discovery, process chemistry and frontloading. The significance of work organisation solutions as a whole is lower, although some particular techniques do have high perceived relevance, while business tools play practically no role at all. So the hypothesis can be considered proven in the original prescription-only business model.
    - The situation is not so clear in the generic prescription only (GRX) model. Here, the significance of the preclinical phase as a whole is smaller, so the

various resource-management solutions are not so strongly "polarised" into relevant and irrelevant groups, either. According to the results of the interviews, process chemistry, which uses scientific and technological solutions, plays a more important role than work organisation solutions, but on that basis, the hypothesis is only partially supported by the evidence in the generic prescription only model. Further interviews may be required to achieve a firmer result.

- Hypothesis H2, namely that "*In the clinical phase of the value chains, the perceived relevance of scientific and technological solutions decreases while that of work organisation solutions and business tools increases."* seems to be substantiated rather than falsified:
    - In the original prescription only (ORX) model, work organisation methods clearly become important in the clinical phase, with scientific and technological solutions occurring embedded in them. Among business tools, strategic pricing and project management are exceptionally important in that phase, which supports the hypothesis.
    - In the generic prescription only (GRX) model, the hypothesis can be formally accepted on the basis of the overall view furnished by the interviews: the role of work organisation solutions does become more important in this model, too, while scientific and technological solutions barely play a role at all in that phase. However, when interpreting the results it must be borne in mind that in the case of equivalent generics, the clinical phase is severely limited, so the results primarily have explanatory power in the cases involving non-bioequivalent or biosimilar drugs.
- According to hypothesis H3: "*After going to market, business tools assume the dominant role in both value chains.*". This was only partially substantiated. It would be more apt to reformulate the hypothesis as follows:
    - After going to market, the perceived relevance of work organisation models does not decrease in the original prescription only (ORX) business model, while that of business tools increases, but even so, in relation to the entire ORX value chain, the significance of efficiency-increasing measures taken in the phases after access to market falls behind that of the scientific and technological solutions and work organisation solutions applied prior to access to market.

- In the generic prescription only (GRX) business model, the role of business tools is more significant overall, but they cannot be said to have a definitive role relative to work organisation solutions, the more likely situation is that they only play a supplementary and supporting role.

- Hypothesis H4: "*In the generic prescription only (GRX) business model, the perceived relevance of business tools lags behind that of scientific and technological solutions and work organisation solutions to a lesser extent than in the original prescription only (ORX) model.*" seems to be clearly correct. The reason for that is presumably that in the price-driven generic markets, the efficiency of daily operation needs to have special attention devoted to it, while the path dependence that characterises the original prescription model is not so dominant there. Still, it must be emphasised that strategic pricing – as a business tool – has greater perceived relevance in the ORX than in the GRX model, which can be regarded as an exception that proves the rule. In fact, overall, strategic pricing seems to be a technique that needs to be treated separately in all significant respects.
- Finally, hypothesis H5, which states that "*Resource management after the product is placed in the market is more significant in the generic prescription only (GRX) business model than in the original prescription only (ORX) model.*" can also be said to have been substantiated on the basis of the above. Still, the results of the research suggest that the truth of the hypothesis is already inherent in the previous hypotheses, so it is somewhat questionable whether this can be considered an independent hypothesis.

6.5 The wider perspective

The results of the present study suggest that the significance of resource management is increasing in the pharmaceutical industry, and in this traditionally technology-driven industry, the work organisation solutions and business tools that are based on the characteristics of the market are coming to the fore. To a great extent, market constraints in the original prescription only and generic prescription only business models that I have examined are represented by the requirements of the financers, with the competition between substitutable preparations being an added element in the case of generics. All of that makes it probable and necessary that in the future, we shall have

to deal more intensely with resource management – the optimal allocation of available resources and the improvement of efficiency – in the pharmaceutical industry.

My research was suitable for demonstrating the specific techniques that can be used along the original prescription only and the generic prescription only value chains in order to improve the efficiency of the allocation of resources within organisations. In that respect, I trust that the survey I conducted – despite the limitations of the methodology based on the 14 in-depth interviews and secondary sources that came to light during the research – approximated a comprehensive view and identified and classified the available techniques correctly. It is obvious, however, that this approach – which examined two segments of the pharmaceutical industry each of which is quite massive, and did so along the entire length of the value chains – is not suitable for an in-depth analysis of the limits and characteristics of application of the individual techniques. It is also clear that the interpretation and evaluation of relevance was not an easily comprehended task for the specialists I questioned, particularly within the framework of one-hour interviews and with the added complication that the terminology that was easily comprehensible and trivial for me (management science jargon) required interpretation for them.

In view of those considerations, I see four possible directions for further work on the basis of the present research, and in fact I believe they should all be pursued:

1. *More exact measurement of relevance:* Further studies with greater accuracy are required about the relevance of individual resource-management techniques. In that respect it is clear that a wider sample of companies could furnish more robust results, and in relation to that the use of questionnaire-based interviews will presumably be unavoidable – a technique I decided not to use for the purposes of my dissertation. Based on the results of my dissertation – in which I was able to identify the resource-management techniques in use with great certainty – it would be possible to prepare a questionnaire that, in addition to asking in person, would also ask about the relevance of the various techniques in a manner that is comprehensible to pharmaceutical specialists. It is probable that such a questionnaire survey – which could only be conducted efficiently by a

research team consisting of several people – would yield a great deal of detail about the factors behind relevance.

2. *Going into greater detail:* During the research I gathered the impression that further drill-down analyses would be desirable in order to explore the special features of individual resource-management techniques. The clinical phase, production, product promotion and sales would all deserve separate studies within both segments of the industry.
3. *Examination of the OTC strategic model:* I believe it would be expedient to extend the present research horizontally by adding an examination of the OTC strategic model. That strategic model is likely to be closer to the generic prescription only segment in terms of general behaviour and the resource-management techniques used, but this would have to be validated by additional research.
4. *The "fourth hurdle" issue:* When using the term "fourth hurdle", the specialist literature of the access to market of original drugs refers to a new precondition of the marketability of drugs in publicly funded markets (in addition to quality, safety and effectiveness – the classic "three hurdles"), namely cost-effectiveness (see e.g. Gulácsi-Boncz-Drummond [2004], Mossalios et al. [2004]). The findings of my dissertation related to original drugs can be interpreted from another perspective as indicative of the fact that the manufacturers subordinate the entire drug development process to meeting the criterion of cost-effectiveness. As one technique for doing so, they register new active ingredients for indications or with prescribed applications that render them cost-efficient relative to existing therapies. Strategic pricing is also shaped accordingly. In addition, within the boundaries of scientific validity, they choose experimental configurations and methodologies that make the drug appear cost-efficient relative to other forms of treatment. It would be interesting to perform a new research project to examine how resource allocation decisions are made during the development and access to market process, which is subordinated to the criterion of cost-effectiveness.

Of those potential directions of research – taking into account the change of emphasis in my own professional interests that has taken place in the meantime – I intend to explore the "fourth hurdle" issue in greater detail in the course of my future research.

Appendix 1: Interrelationship of pharmacochemical technologies and biotechnological methods with the strategy models

It is an interesting paradox of the pharmaceutical industry that while it is one of the most dynamic and technology-intensive industries, until the end of the 20th century its products were developed using cottage industry methods (Gassmann et al. [2008], Sloan-Slieh [2007], Furka [2000]). The *traditional pathway* of molecular synthesis in the laboratory was based on a promising idea, a presumed or real market need or, in many cases on chance, but the essence of it was always that a single development theme always aimed for a *single* small molecule that was imagined in advance to have therapeutic properties and only limited side-effects (Thomke-Kuemmerle [2002] p.623). Although the requirements concerning the physical and chemical properties of the *target* and the *lead* gave direction to the research, the actual compounds were still approached using a method of systematic trial-and-error based on the hypotheses about them. During the approach, every single molecule was synthesized one by one and then it was tested to see whether it would have an effect on the target. The first validation results were practically always negative, so *lead optimization* was commenced, and continued until the validation finally brought a favourable result (Sloan-Slieh [2007], Sweeny [2002], Thomke-Kuemmerle [2002], Furka [2000], Bhalay [1999]).

During that phase, validation and the optimization of the molecule were based on cell biological criteria only, computerized pharmacological (efficacy and toxicological) tests only began afterwards. So in the early phases of development, the exact indication of the molecule was usually unknown: researchers used their resource, intuition and earlier experience to form a hazy idea about what the compound would be good for later on (Sloan-Slieh [2007]).

The trial-and-error method remains a part of current practice, but its efficiency is very low, because a large proportion of the molecules produced prove to be ineffective or only marginally effective, to have side-effects, to be toxic, not sufficiently stable or possibly unsuitable for formulation during the preclinical and clinical tests. On average, one out of five to ten thousand new molecules actually become a medicine[30]; the

[30] Various sources quote various figures. According to Thomke and Kuemmerle [2002] – who refer to an earlier study by Halliday, Walker and Lumley [1992] – on average, one out of 6100 NCEs becomes a

intermediate NCEs are lost from the therapeutic perspective, though the know-how acquired through their development does add to the company's portfolio of intellectual property (VFA [2007] p.28). What's more, the trial-and-error method is also slow – it only allows a maximum of one hundred (!) new molecules to be synthesized per year – and it is also costly. The synthesis, extraction and analysis of a compound – depending on whether it is a fundamentally new compound or only a modification of an existing one – is estimated to take ten to twenty days, while one week of such work costs at least 7,500 dollars (Thomke-Kuemmerle [2002] p.624, Bhalay [1999]).

A great variety of data is available about development costs, sometimes differing by orders of magnitude. The differences are largely the result of differences in the methods of calculations, divergent definitions of the development process or the fact that pharmaceutical development projects show great differences as regards duration and resource-intensity (Gassmann et al. [2008]). One of the most authoritative and oft-quoted sources is the paper by DiMasi et al. [2003], which claims that these days the development of a new drug costs 802 million dollars on average. This figure includes the costs of failed developments as well as a 399 million dollar opportunity cost on the capital invested. The cost of development using this method of calculation was only 54 million in 1979, 231 million in 1987 and 359 million dollars in 1993 (DiMasi et al. [2003] p.154). The tremendous increase was caused by the fact that they had already found the remedies for all basic diseases and researching the remaining ones for which no pharmaceutical treatment is available yet is extremely complex and expensive (Watkins [2002]). In 2001, a study by the Boston Consulting Group put the average cost of new pharmaceutical development projects between 590 and 880 million dollars (CMR [2001b]). A paper by DiMasi and Grabowski [2007] indexed development cost and estimated them at 1,318 million dollars at 2005 prices, and this figure was also taken over by a 2008 publication of the EFPIA (*European Federation of Pharmaceutical Industries and Associations*), adding that a development project takes twelve to thirteen years (EFPIA [2008] p.21, Tufts Center [2008]). Enumerating development costs with exactitude is made more difficult by the difficulty of determining opportunity cost and the fact that companies are 'inclined' to include many items among the costs of the later phases of clinical trials that are in effect marketing costs. (For this dispute, see e.g. Adams-Brantner [2006], Light-Warburton [2005], DiMasi et al. [2004], Watkins [2002]).

The main consequence of the trial-and-error method is that once a manufacturer has developed an effective and profitable medicine in a particular therapeutic area, this generates considerable path dependence due to the accumulated experience and the

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medicine. EFPIA [2008] estimate the same figure to be between 5,000 and 10,000, which agrees with Gassmann et al. [2008] as well. Thomke and Kuemmerle [2002] claim that barely a tenth of the new molecules make it as far as the *in vitro* (test-tube and retort) trials, with only about one fiftieth of those substances going on to *in vivo* animal trials. A higher proportion (about half) of the drugs reaching animal testing are suitable for clinical trials in human subjects, but by that time, the development cost of the compounds that ultimately fail is already huge (Thomke-Kuemmerle [2002]).

capital invested, so *switching costs* are great (Yeoh-Kendall [1999] p.638). It is simpler and potentially more lucrative to remain in the area already prospected and to use the explicit and tacit knowledge already accumulated there (Thomke-Kuemmerle [2002] p.622) to search for better new drugs[31].

It is primarily on the basis of the above factors that the resource-based approach to strategy claims that the resource-based model works well in the pharmaceutical industry[32], while the Porterian model based on market opportunities and gaps is less applicable. In the pharmaceutical industry, the discovery of an unfilled market (therapeutic) gap by a manufacturer is not a sufficient condition for achieving competitive advantages. The development of a product able to fill that gap is a precondition of obtaining those advantages, but that requires know-how, capital, basic research and applied research and development capabilities along with marketing and lobbying capabilities. Those capabilities are usually *valuable, rare, inimitable and nonsubstitutable* resources (Eisenhardt-Martin [2000] p.1105), which each pharmaceutical manufacturer possesses in different forms and to different extents. The existence of those capabilities enable pharmaceutical companies to establish value-generating strategies that make it impossible for new players to enter the originals market (Yeoh-Kendall [1999]). The variable distribution of capabilities among the companies in the industry may provide a possible theoretical explanation for the repeating waves of mergers that characterize the industry.

Yeoh and Kendall divide the strategic capabilities of pharmaceutical manufacturers into two groups: research and development capabilities along with the therapeutic focus are the *component capabilities* that allow the company's resources to be utilized 'locally', in a day-to-day fashion. They claim that capability of drug registration and the capability of radical innovation are *integrative capabilities* and allow the organization to undergo renewal (Yeoh-Kendall [1999] pp.640-641). Thomke and Kuemmerle adopt a similar approach when they emphasize the important role of non-transferable assets and in particular the interdependencies between them for a resource-based analysis of the pharmaceutical industry. For them, an interdependency between assets obtains when investment in one asset results in an increase of the return on the other asset. In their view, such an interdependency exists between the compound library, the molecule screening and the pharmacodynamic research facilities, the information processing capacity and the knowledge of the specialists of pharmaceutical companies (Thomke-Kuemmerle [2002] 621-623).

The path dependence caused by traditional monosynthesis has been reduced by the advance of *combinatorial chemistry*, *computational chemistry*, parallel synthesis and *high-throughput screening* (HTS). Those techniques were originally developed in the

[31] On the other hand, there are also examples of drugs under development proving to be unsuitable for the original therapeutic purposes but effective for other diseases. That is how Viagra (sildenafil citrate**)**, originally developed as an angina medicine, became an effective impotence remedy (Palmer [1999]). However, innovation of that kind, and the resulting switch between therapeutic areas, is not intentional.
[32] See e.g. Barney [1991], Barney [2001], Bates-Flynn [2005], Black-Boal [2004], Grant [1991], as well as my summary paper about the development of the resource-based concept: Dankó [2004c].

mid-1980's for the synthesis of the building blocks of proteins, i.e. peptides consisting of amino acids, but since then they have been applied to most other groups of compounds as well. The essence of these techniques is that based partly or wholly on new technology (solid phase carriers) and approaches (compartment-stirring) they allow the fast and relatively cheap production of a mixture containing many different compounds. The new procedures start with amino acids and first produce dipeptides, then, step by step they keep combining the peptide chains from the previous step into longer chains. This results in the production of large compound libraries a short time: in one week, it is possible to produce a mixture containing several hundred thousand different compounds[33]. Once the mixture is available, so-called *high-throughput screening methods* based on robot technology, semiconductor production technology and nanotechnology are used to select those (bioactive) molecules that affect the target. The continuously developing screening techniques facilitate *targeted screening*, i.e. the specification of parameters that isolate molecules – leads – with a specific required property (Wang [2009], Gassmann et al. [2008], Homon-Nelson [2006], Rabinowitz-Shankley [2006], Sweeny [2002], CMR [2001a], Furka [2000], Berressem [1999], Bhalay [1999], Whiling [1999], Schőn [1998]).

With the advent of combinatorial chemistry and high-throughput screening, the creation of compound libraries and the production of leads has become a great deal simpler, incomparably faster and much cheaper as well over the last decade. The boundaries between therapeutic areas are increasingly permeable and path dependence is reduced. It is important to note, however, that combinatorial chemistry only transforms the research phase. The method is not suitable for speeding up *in vitro* and *in vivo* trials (*lead optimization*), the selected leads can be tested and profiled faster using computer tools (*'in silico'*) (Bowes et al. [2006], Curry [2002], Berressem [1999]). In research, however, combinatorial chemistry has led to a paradigm shift and the time is near when the theorem published by Schőn [1998] that 'launching research projects with a chemical attitude, based on a background in the organic chemical industry is totally obsolete' will become completely true.

[33] The twenty amino acids that constitute peptides and proteins can be linked in any sequence, which means that there are 20^5, that is three million and two hundred thousand different peptides consisting of just five amino acids.

The consequences of the advent of biotechnological methods are equally interesting (see e.g. Arányi [2005]). The application of biotechnology has paved the way towards more effective therapies for diseases that cannot be treated or that can only be treated with poor efficacy using drugs produced using the chemical pathway (e.g. autoimmune and chronic inflammatory diseases, degenerative syndromes of the nervous system, diabetes, etc.). Of the new active ingredients registered today, some 20% are of a biotechnological origin (VFA [2007]), and biotechnology has yielded drugs with very high therapeutic value – although usually rather expensive ones. According to some forecasts, half of all new drugs will be developed using biotechnology within ten years (EFPIA [2008] p.26). Nevertheless, today, biotechnological drug development is a relatively slow and costly methods. The majority of diseases will not be worth treating using biotechnology, so the market of synthetic and semi-synthetic medicines will remain in place in the future (Sloan-Hsieh [2007], Mullin [2002], Sweeny [2002]).

Possible arguments in favour of the spread of biotechnology are as follows:

- Almost 99.9% of the human genome is the same in all people. According to scientists, the remaining 0.1 percent of our genetic stock and the proteins it codes for are responsible for many diseases or at least propensities to disease. Many diseases could be prevented by identifying and 'neutralizing' those genes and proteins. At present, we are aware of some five hundred proteins that may cause disease – in the future, this number could increase to ten thousand. Biotechnology is discovering molecular-level processes that have been hitherto unknown (Malik [2008], Sloan-Hsieh [2007], Sweeny [2002], Jarvis [2001]).
- Biotechnology may be used to manufacture active ingredients – for instance insulin, factor preparations, enzymes – through recombinant methods, with greater purity on an industrial scale whose traditional manufacturing methods are not capable of meeting growing demand (EFPIA [2008]).
- The success of biotechnological research leads to a significant acceleration of preclinical and clinical development, as the protein origin of the drug is reliable proof of its efficacy and non-toxicity (Salvage [2002], Sweeny [2002]).
- The first generation of biotechnological drugs consists of compounds with large molecular weight (>500, oligopeptides, proteins and other large molecules), which cannot be delivered to the body enterally due to their difficult absorption and relative instability. Therefore at present they are administered intravenously, which implies a

deterioration of the quality of life of patients (Mullin [2003]). However, the research aimed at eliminating the problem is promising, and more recently, it has lead to the production of much smaller molecules – antibodies, antibody fragments, peptides (Jarvis [2006]).

However, there are some arguments against the universal utility of biotechnology as well:

- The 0.1 percent potentially defective gene stock is different in every person and the proteins it codes for, along with the syndromes they cause, can be very different as well. This implies that genetic diseases would require personalized drugs. But developing those and selling them in very small quantities would be very expensive – personalized medicines would be prohibitively expensive (Salvage [2002]).
- The production of biotechnological drugs is a complex and costly process that is not equally feasible and/or profitable in all therapeutic areas. The global capacity of facilities suitable for the production of biotech drugs is also rather limited at present (Hine-Capeleris [2006], Sweeny [2002]).

Based on the above arguments and the sources I've referred to, the development of pharmacochemical technologies and the gradual spread of biotechnological drug development may influence the strategic behaviour of pharmaceutical companies. The refinement of the techniques of combinatorial chemistry, high-throughput screening and profiling shall reduce the traditional path dependence of pharmaceutical companies and shall increase the permeability of borders between therapeutic areas. The advent of biotechnology shall shift the focus of research somewhat and it shall open up perspectives that may result in a reorganization of competitive advantages as well. But such reorganization is by no means without its constraints:

- firstly, innovative methods tend to be effective if they build on the experience that the pharmaceutical companies have already accumulated in the therapeutic field concerned, which implies that the sheer acceleration of pharmaceutical research shall not result in a radical increase in transfers of know-how between individual therapeutic fields or indeed the rapid disappearance of boundaries between them;
- secondly, biotechnological competency within the organizations of large pharmaceutical companies are traditionally weak, which has had and still has the result that biotechnological development usually takes place in the form of

partnerships between specialized biotech companies and pharmaceutical companies that are well acquainted with the regulations governing clinical trials and registration and which are also able to finance those rather costly phases. As a result, large pharmaceutical companies are removed from basic research, outsource their previous strategic capabilities and increasingly turn into registration, marketing and sales apparati.

In view of all that, in the present dissertation I shall adopt the view that although the above two factors do have an important effect on the strategies of pharmaceutical companies, they do not lead to independent strategy models, not even in the case of biotechnology.

Appendix 2: Specific value chain of the OTC strategy model

Of the three specific value chains, the one belonging to the OTC strategy model is the simplest, as shown in *Figure F-1* below:

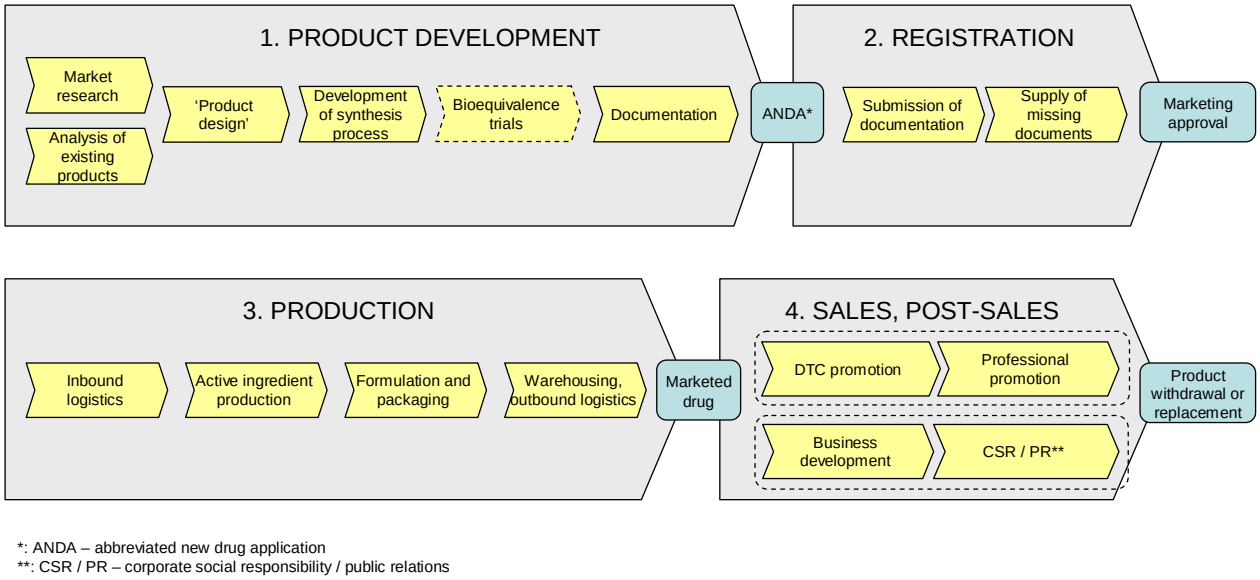

Figure F-1: Specific value chain for the OTC strategy model

The main differences relative to the generic value chain are summarized below:

- In the case of the OTC strategy model, it is more correct to speak of product development, which includes all steps of development from the initial decision to the compilation of the registration documentation. Product development may include the further development of existing compounds or the mixing of existing products (mixtures of active ingredients and excipients).
- OTC products are usually not subject to limited preclinical or clinical trials. The simplicity of product development, the minor changes in biological effect, the relatively small number of possible active ingredients and the widely documented nature of these products result in only bioequivalence tests being conducted, if required.
- In the case of OTC products, marketing has two major directions as, in addition to professional promotion and communication there is also an opportunity for direct-to-consumer (DTC) promotion. This may take place at pharmacies or, with some

legislative constraints, outside pharmacies as well. Marketing activities are generally launched after the marketing approval is granted.

- With the exception of special cases, patent infringement lawsuits are not characteristic of the OTC market, so marketing does not perform that set of tasks.
- The life-cycle of OTC products ends when the product is removed from the market (and its registration is cancelled) or when it is replaced by other preparations.

The time requirement of molecular development – including development of the production technology and the performance of bioequivalence tests – is 18 months on average, though some variations are possible. The application for registration is usually assessed in a relatively short period of time (less than 1 year), with little variation.

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- Act No. XCV of 2005 about medicines for use in human beings and the amendment of other acts regulating the pharmaceutical market ('New Drug Act')
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- Decree no. 35/2005 of the Ministry of Health about the clinical testing of experimental preparations for human consumption and the application of Good Clinical Practice
- Decree no. 44/2005 (X. 19.) of the Ministry of Health about the personnel and material conditions of manufacturing drugs for human consumption
- Decree no. 52/2005 (XI. 18.) of the Ministry of Health about the marketing of drugs for human consumption
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