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Letter from the Editor

Expect the Unexpected

Companies are continuously confronted with several challenges, such as financial straits, changing customer needs, new competitors, increasing raw material prices, or ecological changes. Although these are only general topics representing potential threats, there is one clear message for companies: expect the unexpected! Especially unexpected changes in a firm's environment lead to one tough challenge, namely the trade-off between being agile and efficient at the same time. Companies, for instance, need to be agile and adaptable to changing customer needs. Therefore, they may not only focus on present customer needs, but also on future and unaware needs of their customers. Simultaneously, organizations, driven by cost saving requirements, need to improve their operational efficiency. Besides handling such a trade-off, firms additionally need to invest into R&D activities in order to be prepared for changes. Especially in research intensive industries such as the chemical or pharmaceutical industry, R&D investments are essential, since the development of new technologies represent the most reasonable opportunity to suc ceed in the market place. Therefore, we are pleased to present you some new insights related to the management of technology licensing, the effects of the global crisis on the management of small firms, the development of integrated production networks as well as managing personalized medicine.

In our first research paper "Management of technology licensing as a foreign market entry mode: The case of leading Italian pharmaceutical and biotech companies", Uros Sikimic, Federico Frattini, and Vittorio Chiesa explore managerial aspects that are required to handle technology licensing in the specific case of entering foreign markets. Here, they rely on a multiple case study research approach including cases of Italian pharmaceutical and biotech companies. Their key findings can be summarized into two points, i.e. (1) in order to manage technology licensing as the foreign market entry mode firms refer to the process view perspective and (2), in so doing, these companies tend to develop dynamic capabilities.

Cezar Scarlat examines, in his article "The influence of the global crisis on the management of the small firms active in the Romanian pharmaceutical industry", how the recent economic and financial crisis has influenced the management of Romanian small and medium size enterprises operating in the pharmaceutical sector. His conducted survey, based on 375 respondents, entails that early reactions to the global crisis were reported as early as August 2008, which increased to an absolute maximum in March 2010. Furthermore, the author identified that the smaller the company size, the slower the reactions. If a strategy could be identified, most of the SMEs acted rather defensive, i.e. change of product range, changes in strategic alliances or retrenching.

In our first article for the practitioner's section, "Development of integrated production networks using extended material flow analysis", Marco Auer analysis the use of extended material flow analysis in order to predict the effect of changes in production networks. Especially in the case of chemical companies, the appropriate implementation of integrated production networks may represent an opportunity to gain competitive advantage. In his work, Marco Auer starts with a material flow analysis and extends this approach with cost and investment analyses while using scenario techniques. In so doing, an optimized configuration of the network can be identified. For his analysis, the author applies a simplified case study related to the Mueller-Rochow Direct Synthesis.

In the paper "Personalised medicine, unmet need or business strategy?" Graciela Sáinz de la Fuente uses the case of Thiopurine Methyltransferase (TPMT) testing to illustrate the reasons why personalised medicine for off-patent drugs is less used at a clinical level than personalised medicine for drugs under development. More specifically, the author analysis the technological trajectory of TPMT testing and the process of clinical uptake by the UK National Health Service (NHS). In so doing, main enablers and barriers during the introduction of TPMT testing in the NHS are identified.

Now, please enjoy reading the first issue of the ninth volume of the Journal of Business Chemistry. We would like to thank all authors and reviewers who have contributed to this new issue. If you have any comments or suggestions, please do not hesitate to send us an email at: contact@businesschemistry.org.

Carsten Gelhard, Executive Editor
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Journal of Business Chemistry

Research Paper

Management of technology licensing as a foreign market entry mode: The case of leading Italian pharmaceutical and biotech companies

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Technology licensing has been recognized for decades as one of the new market entry modes. Companies often issue licenses in foreign countries in order to enter a new market. This paper aims to unearth how companies manage the technology licensing, purposely used by firms in order to enter new markets. Starting from the perspectives given in the Dunning's eclectic theory on foreign market entry modes, and by adopting the process view perspective from the technology management literature, and also incorporating the Dynamic Capabilities Framework, this paper tries to explain the managerial aspects of technology licensing as the foreign market entry mode.

Although technology licensing as a market entry mode has been previously thoroughly explored, limited attention has been given to the possible ways companies approach in managing technology licensing for the new market entry purpose. In the paper authors rely on the multiple case study research approach in order to reveal the relevant managerial aspects implemented by Italian pharmaceutical and biotech companies that exploit technology licensing for the new market entry purpose.

The key findings in this paper indicate two points: (i) companies adopt the process view perspective for managing technology licensing as the foreign market entry mode and (ii) throughout the stages of this process firms tend to develop their dynamic capabilities (sensing, seizing and reconfiguring). These research findings contribute to a deeper understanding of technology licensing as a market entry mode in the Innovation and Technology Management literature, but also in the Internationalization literature, by integrating the elements coming from these two research streams. The managerial implications resulting from this paper may be especially useful for the firms operating in the research intensive industries (like chemical, semi-conductor, biotech, etc.), enabling them to recognize the relevant issues in technology licensing process for the market entry purpose.

1 Introduction

While competition has rapidly become knowledge and technology based, companies need to effectively manage their technological assets in order to realize any potential inherent in their intangibles

and to benefit from their innovation investments (Chesbrough, 2003; Teece, 1986). Ford (1988) proposed technology licensing as one of the forms for exploiting technology, where knowledge is the economic good exchanged, in the form of technologies, patents, ideas and know-how (Grandstrand, 2000). This research concentrates on technology licensing (further on called licensing), which may be motivated by some monetary and non-monetary drivers, enabling firms to realize a new market entry (Koruna, 2004b; Reitzig, 2004; Arora et al., 2001; Grindley and Teece, 1997; Veugelers and Cassiman, 1999). Practically, licensing for the market entry purpose reduces the entry costs when accessing a market (Fosfuri, 2004; Birkenmeier, 2003).

Guadamuz (2005) defined technology licensing as "the transfer of technology by means of a contract of industrial property rights". Moreover, a licensing agreement may also transfer protected or unprotected know-how, training of specialists, transfer of procedures and technical assistance. Licensing agreement is a result of technology licensing and it is constituted by a sourcing firm purchasing the rights to another firm's patents or technology for a lump sum payment and/or royalties (Hagedoorn and Hesen, 2007). Licensors are firms that own the essential patents and licensees are firms that purchase the right to use these patents (Joshi and Nerkar, 2011). Particularly, this paper explores the use of licensing for the foreign market entry purpose.

Researchers claim (Bianchi et al., 2009; Birkenmeier, 2003; Escher, 2003) that the main barrier to the successful licensing is a lack of appropriate management of it. Licensing management explores all the managerial activities that companies deal with when engaged in technology licensing. There are firms that experience considerable managerial difficulties with it, whereas others realize enormous benefits (Elton et al., 2002; Lichtenthaler and Ernst, 2006, 2007). Research on the management of technology licensing activities is still relatively limited and previous works do not address particularly the managerial challenges (Nakamura and Odagiri, 2005). Some research gives insights on the aggregated industry level, but do not explore closely how do firms manage their technology licensing activities (Anand and Khanna, 2000; Arora et al., 2001). There are works that have previously focused on the licensing outcomes, but have not concentrated on the managerial activities leading to these outcomes (Kim and Vonortas, 2006; Nagaoka and Kwon, 2006). However, as far as the authors' knowledge, none of the previous works explore the management of technology licensing, observed as a new market entry mode.

This article aims to give a first step towards closing the research gap in the research on technology licensing as a market entry mode, by addressing the following question: *How firms manage their licensing activities, used in order to enter foreign markets?* This question is explored by analyzing the empirical evidence coming from explorative case studies from the four leading companies in the Italian pharmaceutical and biotech sector. The paper starts from the Duning's OLI framework from the market entry mode literature, combined with the process view perspective from the technology management literature and some elements introduced in the Dynamic Capabilities perspective. The key findings indicate two points: (i) companies adopt the process view perspective for managing technology licensing as the foreign market entry mode and (ii) throughout the stages of this process firms tend to develop their dynamic capabilities (sensing, seizing and reconfiguring).

This article is structured as follows. The second section will give some theoretical foundations from the relevant literature. Section three will explain closer the research approach and the methodology applied. In section five the main findings will be discussed. Section six will conclude with the main ideas deriving from the paper and with the possible directions for the future research. The outputs of a research target at developing a systematic analysis of the critical managerial issues to be faced during technology licensing as the market entry mode.

2 Literature Review

Starting upon the definition of technology licensing given by Guadamuz (2005) ("the transfer of technology by means of a contract of industrial property rights"), a brief literature is given on management of technology licensing used as a foreign market entry mode. In this context, the technology management and the foreign market entry mode literature were reviewed.

2.1 Technology Licensing in Technology Management Literature

There are many works on technology licensing, which are sole theory and do not address managerial challenges (Nakamura and Odagiri, 2005). In order to manage licensing properly, researchers stress the importance of strategic openness in the firms (Chesbrough, 2007; Davis and Harrison, 2001). Companies should be shifting from closed to open licensing strategy (Chiaroni, et al., 2010), which does not limit licensing activities only to the transfer of internally unused technology (Dodgson et

al., 2006; Prugl and Schreier, 2006), but employs an active licensing with clear strategic goals. Another point states that companies should establish a formal licensing strategy (Pitkethly, 2001; Davis and Harrison, 2001; Rivette and Kline, 2000), used as a tool for achieving monetary and strategic benefits. There are papers indicating that companies need to implement an active strategy, where they actively seek for licensing opportunities (Fosfuri, 2006; Kim and Vonortas, 2006). Several authors support the notion that inter-firm collaboration has shown that managing technology transactions requires a process view (Bianchi et al., 2009; Hoffmann, 2005; Chiesa and Manzini, 1998). Similarly, some researchers highlight the importance of a systematic licensing process, which may start upon the technology sale process from Chiaroni, et al. (2010). In essence, the idea is to systematize the technology licensing process in several stages and to facilitate management of its activities (Koruna, 2004a; Tschirky et al., 2004). The industry experts and the indications from the researches agree on the fact that a formalized process is important, although the specific number of process stages may vary (Ernst, 2002; Cooper and Kleinschmidt, 1995). Accordingly, this process does not usually follow all the steps sequentially, but iteratively including feedback loops and reiterating some phases. In the Chiaroni et al. (2010) paper, the major steps of the technology sales process are planning, intelligence, negotiations with potential licensees, technology transfer, and control. Each stage is comprised of specific managerial challenges and main tasks to be performed. These activities are usually complex, differing in every licensing case, and need to have a systematic management that will consider the entire process. The process aims to allow companies to achieve an optimum management of all activities in licensing. So, licensing as a mode for the foreign market entry can be approached as a managed and structured process with the clear aim.

As managerial and organizational processes lead to the development and deployment of firm's dynamic capabilities (Helfat et al., 2007), management of the process of licensing within the firm is closely related to its dynamic capabilities development and deployment. Teece (2007) explains that the dynamic capabilities framework entails the following components: sensing opportunities and threats, seizing opportunities and reconfiguration of resources. By structuring the technology licensing process, the abilities of companies to sense, seize and reconfigure, are being developed and enstrengthened. Initially, the dynamic capabilities approach was made for analysis of the sources of wealth creation and capture by firms (Teece et al., 1997). The Dynamic Capabilities Framework showed that companies need to align their resources with the demands of the market through sensing, seizing and reconfiguring activities (Teece, 2007). Firstly, firms need to focus on sensing activities, which are seen through seeking for the new opportunities. Previous works state that the basic routines of the sensing capability are: (i) generating market intelligence (Galunic and Rodan, 1998) and (ii) disseminating market intelligence (Kogut and Zander, 1996). In this phase, companies scan, explore and analyze the information from their surrounding and in this manner discover existing and create new opportunities. Bianchi et al. (2010) develop a step-by-step methodology, based on the TRIZ idea, for the identification of opportunities for licensing a firm's technologies outside its core business, which fits the purpose of the sensing phase. Moreover, firms must manage and filter the information, which will enable them to identify the information of interest (Ocasio, 1997). Secondly, the seizing the opportunity follows, which is related to pursuing of the new initiatives (Van den Bosch, Volberda and De Boer, 1999) and seizing opportunities (Teece, 2007), by considering acquiring, assimilating, transforming, and exploiting knowledge (Zahra and George, 2002), and responding to market intelligence (Teece, 2007). Thirdly, after sensing and seizing the opportunities, the reconfiguration of resources initiates. Among others, reconfiguration is accomplished by managing strategic fit of the process, observing the appropriateness matters (Galunic and Rodan, 1998), timeliness matters (Zott, 2003) and efficiency matters (Kogut and Zander, 1996). This research analyzes whether the process view of technology licensing used for the foreign market entry purpose allows firms to develop the three dynamic capabilities.

2.2 Technology Licensing in Foreign Market Entry Mode Literature

Most of the international business literature examines licensing in the new market entry modes context (Aulakh et al., 2009). In the research on the internationalization process models, academics observe licensing from the transaction costs perspective and usually compare its efficiency with other foreign market entry modes (like exports, joint ventures and wholly owned subsidiaries (Anderson and Gatignon, 1986; Buckley and Casson, 1976; Contractor, 1984)). In general, this literature sees licensing as a low-commitment/low-return entry mode, which companies use primary to acquire some experiential knowledge on the foreign markets before they continue further to commit to this new market (Arora and Fosfuri,

2000; Johanson and Vahlne, 1977). Initially licensing was mainly applied as an alternative strategy to FDI (Brouthers and Hennart, 2007; Goldscheider, 2002). Increased competition and faster product and technology cycles have led companies to make a thorough evaluation of their technology portfolio, considering licensing as a commercialization strategy to generate additional revenues at almost no additional cost. When the choice of the market entry mode is in question, licensing is viewed as a low investment, low risk/return alternative which provides least control to the licensing firm (Woznick, 1996; Agarwal and Ramaswami, 1992). This experiential knowledge of a foreign market is especially valuable because some authors argue that net profit resulting from the licensing transaction and received by the licensor is lower than the net profit received by keeping the technology in-house or licensing it to a firm's subsidiaries (Kotabe et al., 1996). Authors explain that the major reason for this is seen in high transaction and opportunity costs coming from the technology transfer to other firms. Dunnings' OLI eclectic paradigm, extensively used to compare the foreign market entry mode choices (Terpstra and Yu, 1988; Sabi, 1988; Kogut and Singh, 1988; Davidson and McFetridge, 1985; Caves, 1982; Dunning, 1980), puts a strong emphasis on factors influencing the preference for licensing versus FDI to enter foreign markets (Dunning, 1993). Dunnings' OLI eclectic paradigm analyzes the foreign market entry mode choices decisions in terms of ownership (O), location (L), and internalization (I), or OLI. Each one of the OLI factors has been associated with precise advantages that can enhance the firm performance. Further on, researchers present licensing as the second-best entry strategy, which primarily enables companies to extract residual value from mature technologies (Telesio, 1979).

However, firms increasingly rely on licensing to enter foreign markets and gain global competitive advantage (Fosfuri, 2006; Hill, 1992, 1997; Kotabe et al., 1996). Only limited attention has been paid to management activities of licensing as a mode of entry, which can provide with an option to grow when uncertainty is resolved favorably, while also offering enough flexibility to abandon the market in the event of negative information (Ahsan and Musteen, 2011). In this sense, an important issue not studied thoroughly in the foreign market entry mode literature should answer questions on ''how to license'' in the foreign markets rather than ''whether to license'' (Aulakh et al., 2009). Similarly, in this work authors implement the OLI perspective in the technology licensing management, which companies exploit when engaged in licensing for the foreign market entry purpose.

The literature review on technology licensing in technology management literature and foreign market entry mode literature, points out on a gap in the previous research, not explaining the managerial activities encountered by the companies that engage in technology licensing for the foreign market entry purpose. In order to untangle this overlooked issue, this research observes the case studies originating from the leading Italian pharmaceutical and biotech companies that engage in licensing for this purpose. The analysis adopts several ideas from the reviewed literature, like the process view of licensing aligned with the Dynamic Capabilities framework and Dunnings' OLI eclectic paradigm. The next section provides more detailed information on the methodology applied.

3 Methodology

For the purpose of this research comparative multiple case studies were applied (Yin, 2003), because they enable an in-depth examination of each case and also enable a cross-case comparison (Eisenhardt and Graebner, 2007). As explained in the previous sections, this paper is more focused on answering 'why' and 'how' research questions, which suite this methodology (Eisenhardt, 1989). Different forms and approaches to the management of licensing as a foreign market entry mode have not been significantly documented, which can be appropriately investigated and presented with a qualitative approach. Relying on the theoretical sampling logic given by Siggelkow (2007), this study has chosen to observe four leading Italian pharmaceutical and biotech firms. The pharmaceutical and biotech industry was chosen, because these industries indicate a strong presence of active licensors (Schilling, 2009; Kim, 2009; Arora and Ceccagnoli, 2006; Rivette and Kline, 2000; Grindley and Teece, 1997). Importantly, there is an active market for technology in the chemical processes (Arora et al., 2001). When setting up selection criteria on whether to include the company in the research, the following was accounted: (i) selected companies have been identified as active licensors (ii) selected companies have already been engaged in licensing in the foreign markets; (iii) sample of companies was not limited to any firm size. The "polar type" sampling procedure (Eisenhardt and Graebner, 2007) was not used, because it was not necessary for the purpose of this research. The overall performance of licensing was not an issue of interest here, but the managerial activities met during technology licensing for the foreign market entry purpose. However, pure theoretical sampling was enough to allow experimental situa-

tion, where the phenomenon of interest was studied under particularly insightful circumstances (Siggelkow, 2007). Finally, research results coming from the exploratory case study analysis are not statistically generalizable (Yin, 2003), but exploratory. The overall goal is analytically and theoretically to combine the existing body of knowledge on technology licensing management from the technology management research and research on technology licensing coming from the foreign market entry literature, in order to build a basis for future theoretical and empirical studies on technology licensing management used as the foreign market entry mode.

Preliminary list contained ten companies that may fit the explained selection criteria. These firms were identified in consultation with the experts from the Licensing Executives Society Italia (LES Italia), a nonprofit organization that operates in the field of business law, intellectual property and technology licensing, trademarks and intellectual property. LES Italia has more than 300 members, representing the largest firms, industrial organizations, research institutes, law and patent firms that aim to promote opportunities for licensing. Afterwards, each of the firms was contacted in order to gather information on the company and to make and additional check whether it fits the sampling criteria defined. Eventually, the final sample comprised of four firms that met all the criteria stated above. In Table 1 some preliminary information on the companies included in the sample are provided.

In the data collection procedure, the research mainly relied on the semi-structured personal interviews with the key informants. All the interviews were conducted in the period between the January 2012 and May 2012. In each company the interviewed persons were heads of licensing units. If the firm didn't have a dedicated licensing unit, either responsible person for the management of research and technology, or person responsible for

Table 1 Preliminary Information on the sampled companies.

Firm	Sector	Total turnover[a] (# employees)[c]	# of patents (# licensing agreements)[b]	Interviewed personnel
Company A[1]	Diagnostic	1.000.000 (3000)	1500 (N.A.)[d]	- Integrated Research Director - Technology Opportunities Director
Company B	Pharmaceutical	68.000 (280)	7 (60)	- Head of Licensing & Business Development - R&D Director -International Sales Manager
Company C	Biopharmaceutical	529.000 (800)	308 (N.A.)	- Marketing e and International Sales Director - Head of Licensing Unit
Company D	Pharmaceutical	500.000 (2000)	258 (50-60)	- Head of Business Development

[1] The names of the firms were omitted on purpose, as the interviewed personnel request.
[a] Total turnover in thousands of euro, as of 2010 (source: interviews and company archival data).
[b] Number of patents and number of licensing agreements (source: interviews, company archival data and company website).
[c] Calculated as full-time equivalent employees.
[d] N.A. = not available.

the international markets was interviewed. In all the cases a second person, generally from R&D or marketing department, was interviewed in order to obtain a different assessment. Moreover, at least one member of the top management team (if present) was interviewed for each firm. A minimum of three interviews for each company was made and a total of thirteen thorough face-to-face interviews were used as a basis of this research. Interviewing multiple respondents from each of the firms was done with the aim to accomplish data triangulation and to reduce the retrospective and personal interpretation biases. All the interviews lasted between 1 and 3 hours, they were digitally recorded and manually transcribed by typing all the interviews in the digital form. For this purpose computer software called Express Scribe has been engaged. Express Scribe is professional audio player software designed to assist the transcription of audio recordings, which enables controlling audio playback using a transcription keyboard (with "hot" keys). This software was particularly useful, while it enabled valuable features for transcribing (like variable speed playback, multi-channel control, file management, etc.).

Importantly, the documented information on the management of technology licensing for the foreign market entry purpose, but also general data on the company, were collected through secondary sources (like internal documentation, project reports and company web site). All the multiple interviews and the documented data collected were primarily used to triangulate the information gathered. The Appendix A presents the major topics of interest and the open-ended questions asked during the interviews. All the major topics and the open-ended questions from the Appendix A have served as a research protocol, allowing the interviewer to

Table 2 Operationalization of the dynamic capabilities (relying on some elements from the work of Pavlou and El Sawy, 2011).

Capability	Brief Description	Code	Basic Routines to identify
Sensing	Spotting and interpreting the opportunities	1.1	Generating market intelligence (Galunic and Rodan, 1998)
		1.2	Disseminating market intelligence (Kogut and Zander, 1996)
Seizing	Seizing and pursuing the opportunities	2.1	Acquiring, assimilating, transforming, and exploiting knowledge (Zahra and George, 2002)
		2.2	Responding to market intelligence (Teece, 2007)
Reconfiguring	Reconfiguring assets	3.1	Appropriateness matters (Galunic and Rodan, 1998)
		3.2	Timeless matters (Zott, 2003)
		3.3	Efficinecy matters (Kogut and Zander, 1996)

lead a semi-structured examination, but also to keep the record of the interview procedure in the case of replication or extension of the analysis (Yin, 2003).

When the data analysis started, firstly the collected information was manipulated by relying on the data categorization and contextualization techniques (Miles and Huberman, 1999). Secondly, the structured data analysis process was followed. This process consisted of a preliminary within-case study and an explanation building investigation, followed by a cross-case comparison. The investigation in this research initiated by inducing whether the companies from the sample applied any structured process like approach in managing licensing as the foreign market entry mode, which was suggested in the literature review section. In order to check if within this licensing process in the companies some of the elements of Dynamic Capabilities Framework were recognized (sensing, seizing and reconfiguring) and developed, the Dynamic Capabilities Framework had to be operationalized by giving a set of activities that characterize each of the dynamic capabilities. In Table 2 the list and codes of these activities and criteria were provided, which was derived from the analysis of the dynamic capabilities literature.

This operationalization was applied to identify whether through the licensing process for the foreign market entry purpose, firms develop these dynamic capabilities. The structured procedures for data collection and analysis, but also the semi-structured interviews, were used in order to enhance the reliability of the research (Yin 2003). Table 3 (in the Appendix B) presents the brief description of the companies studies, their examples of licensing projects as the foreign market mode and describes the licensing phases identified.

4 Results and Discussion

This section presents and discusses on the main findings from the case studies. Table 4 (given in the Appendix B) gives the results of the analysis of all the process in order to identify the dynamic capabilities developed along the process. All the companies involved in the research, recognized within their foreign market entry strategy a strong exploitation of licensing for this purpose. Integrated Research Services and Technology Opportunities Director interviewed in front of the Company A explained that operating on a global scale is not just a choice but also a necessity, because innovation in pharmaceutical industry is costly and long lasting, and the only way to obtain the return of investment is to launch it on a world wide scale. On average it takes 12 years from beginning of the development to the market approval, costing between $0.8-1 billion (Austin, 2006), and with high attrition rate that allows only 2-3% of products to actually be launched on the market),The findings do not aim to categorize, but to present the content of the managerial activities coming from the technology licensing process as the foreign market entry mode. The process perspective helps academics to study, but also practitioners to carry out, the management of technology licensing as the foreign market entry mode.The interviews performed confirm that the phases taken from the paper of Bianchi et al. (2011) considerably reflect the proposed process stages. Furthermore, within the context of this process some elements of the Dynamic Capabilities Framework have been recognized, pointing out that this process like approach enables development of the dynamic capabilities for this purpose.

4.1 Planning

In the companies examined, the planning stage does not have any observed specificities and it is considered to be a part of the process of building the company's strategy to internationalize on foreign markets. The reason for this finding can be explained by the fact that in the choice of the sample, firms that already engage in active licensing and engage in licensing in the foreign market have been examined. So, they do not have the planning phase, because in their case it is already implemented in their overall company strategy. The alignment between the overall firm strategy, and internal and external exploitation programs is the main activity actually performed in the planning stage. In the interview with the Head of the Licensing Unit in the Company D, she explained that her company has already developed strategy to rely on technology licensing for the foreign market entry purpose and that the whole process initiates with data collection on the foreign market.

4.2 Intelligence

This phase of the process has in previous studies been characterized by the technological and market environment scan, the sale opportunities identification, and the contractual mode choice (Bianchi et al., 2011). When companies involved in this research decide to enter the foreign market they firstly start with the ***market seeking*** on which market to enter and afterwards with ***partner seeking*** within this market. Similar concept has been recognized with other authors, explaining that licensing is shaped by industry level and market level related concepts (Walter, 2012). Partner see-

king has been identified within the intelligence phase of other similar research works (Bianchi et al., 2011) and has been considered as highly important. Further on, when they involve in the ***market seeking***, companies closely process the following parameters:

- **Freedom to operate:** an in-depth study of the state of the art in patents in order to check if there is a already present on that market (see e.g. Company A and B);
- **Exclusivity:** evaluation of the exclusivity of their product; whether firm can attain the allowance to produce and sell the product; presence and availability of similar products on the market (see e.g. Company A and D);
- **Cultural differences:** observing how the general business culture in the country fits firms' ideas for that market; if the cultural differences may facilitate or aggravate their presence in the market (e.g. Company A managers give an example of Japan, where the employees are loyal to the country on the first place, and afterwards to the company, see also Company B);
- **Market size:** see e.g. Company B and D.

The market analysis is the foundation for the ***partner seeking***, which includes the evaluation of the following features of potential partners:

- **Financial capabilities:** financial foundations, sales, company size (e.g. Company B states that long decision timing in bigger companies may make problems), see e.g. Company A, B, C and D;
- **Technical capabilities:** portfolio of products, possibility for cross-licensing, degree of specialization (e.g. when Company B licensed the product for tumor in Canada, they explored the companies that are active only for this specific tumor), experience (see e.g. Company A, B, C and D);
- **Commercial capabilities:** presence in the field, location of a partner (e.g. Company A manager explains that suitable partners are in Princeton, New Jersey, where the majority of world pharmaceutical industry is based and it is close to university), presence in other markets (e.g. Company C was seeking for a partner in Russia that was also present in other former Soviet Union and Eastern European markets), see e.g. Company A, B, C and D.

Interestingly, the Company C has a fully formalized intelligence process that has a step-by-step procedure for the market analysis and the partner analysis, based on the evaluation of potential markets and partners. The management of this process is lead by the dedicated functional unit, specialized for the market intelligence, suggested by other authors as well (Kale et al., 2002; Bianchi et al., 2011A). This process initially aims to build a "Long List" of pharmaceutical companies belonging to the main National Trade Associations, after which the public available information relevant to assess partner's "generic and specific requirements are being gathered. Company C then filters the data collected, firstly by excluding the companies with an unfitting business model. The unfit companies are recognized as the ones that base their business on the generic drugs production, on the offer of specialized R&D services, on exploitation of the plain homeopathic treatment ideas, etc. In the next step the in depth desk analysis and profiling of the short listed companies is done by ranking of the short listed companies. In the ranking Company C observes their Product Portfolio Fit (therapeutic field, number of drugs, the expertise they have on the regulatory activities, presence in other markets) and Economic and Financial Soundness (financial foundation of the company). This procedure, in the abstract level, may be employed in other industries as well.

After the analysis of the interviews with the managers, a strong presence of the routines that develop the sensing dynamic capabilities has been noticed. 100 percent of the companies from the sample appear to be relying on the routines for generation of the market intelligence (Galunic and Rodan, 1998) and dissemination of the markets intelligence (Kogut and Zander, 1996).

4.3 Negotiation

The negotiation stage introduces the communication with the partners with the intention to sell the technology and to establish the contractual agreement (Bianchi et al., 2011). Negotiations include several aspects that companies manage when they rely on licensing in order to enter a foreign market. It is considered as a particularly risky stage, because companies need to disclose certain information on their technology in order to negotiate on the technology sale. The person from the Company A responsible for managing the Technology Opportunities Department sees this phase as a "complex process within the process, which needs to be managed extremely cautiously ". All the negotiations are performed in multiple stages manner (see e.g. Company B) and they are concentrated around:

- **Commercial aspects:** dealing with financial indicators and returns (see e.g. Company A, B and D);
- **Technical aspects:** questions of approval for the product on the market, timing and cross-licensing (see e.g. Company A, B and D).

It is important to stress that companies often engage in "multiple- negotiations" (like in the case of Company A). This situation is common when there is a need for so called "stacking provision", which appears when a certain owner of a patented technology intends to manufacture products under the license and for this purpose it needs to obtain additional licenses from other parties who own rights in related, actual or potentially overlapping technologies. This is a case when a company has to negotiate with more companies whose patents they need for production of the current product or whose patents overlap to some extent. In any case in the negotiation phase firms can practice some methodologies that facilitate the overall negotiations (like the Thompsons' (2011) mixed-motive negotiation techniques and some practical intangible-asset evaluation methods reviewed in the paper from Smith and Parr (2000)).

The negotiation stage also allows enterprises to build up their seizing dynamic capabilities. For instance, companies A, C and D, show the significant presence of evolution of their acquiring, assimilating, transforming, and exploiting knowledge activities (Zahra and George, 2002), and market intelligence response activities (Teece, 2007). By definition, the seizing dynamic capability perfectly fits into the main goals of the negotiation stage of the process, but our analysis also puts forward the notion that the presence of routines that enable and expand this capability is identified in the realization stage (like in the example of the Company C and Company D). Nevertheless, in 75 percent of the companies (Company A, B and D) seizing dominates the negotiation stage, and in 50 percent of the companies (Company C and D) it has been also identified in the realization stage. In one firm (Company D), the negotiation phase has an important role for the deployment of the reconfiguration capability in the firm.

4.4 Realization

After intelligence and negotiation firms arrive to the realization phase, involving the actual transfer of technology between the counterparts (Bianchi et al., 2011). The major hindrance appearing here is caused by the tacit nature of knowledge, which is difficult, long-lasting and expensive to transfer. So, the managers from the firms studied try to circumvent this obstacle by continuing to provide the support to the partner company even after the transaction has officially been completed. In this manner, partnering firms' business and treatment of the licensed technology is backed up by the licensor firm. The realization stage in licensing process for the purpose of the foreign market entry includes the two aspects:

- **Technology transfer:** seen as pure transfer of know-how and the supporting documentation (Company A, B, C and D);
- **Marketing support:** for instance, Company C makes a detailed marketing support for the partnering company, containing the information and knowledge to enter the market (similar point observed in the Company D).

This marketing support gives closer explanations on the experience of the company and their previous partners in the foreign markets. It is made with the aim to help partners in the new markets to understand how the product works and what its benefits on which they should focus are. The marketing support is transferred to partnering company through trainings, seminars and written documents (similar point observed in the Company D).

This stage enables the development of the seizing dynamic capabilities. In 50 percent of the companies realization stage gives firms an opportunity to develop their seizing capability. Seizing and reconfiguring capabilities are more active and operational capabilities in the company. So, it may be concluded that the actual realization phase advances these two, operational capabilities.

4.5 Control

As stated in Bianchi et al. (2011) work, the control stage entails the monitoring of the partner's behavior and compliance with the contract. In the licensing process used for a company to enter a foreign market, two main points are controlled after the realization of the technology transfer and marketing support. These points include:

- **Contract management:** introduced the control of the terms given in the contract, which include the respect of intellectual property aspects and the respect of the outlined commercial arrangements (like the achievement of the minimum quantities of sales and fulfillment of the time framework given in the contract, as explained by Company B, C and D);
- **Alliance management:** concentrated mainly on the monitoring the heed of the commitments of the partner company (see e.g. Company B and C).

Both of the points presented above are controlled on a pre-defined periodic basis relying on conference calls, meetings, additional trainings and written reports. The question of the size of the partner company has a strong impact on the control phase. Head of the Business Development in Company D explains that bigger companies are more autonomous are and more difficult to follow.

Control phase of the licensing process has allo-

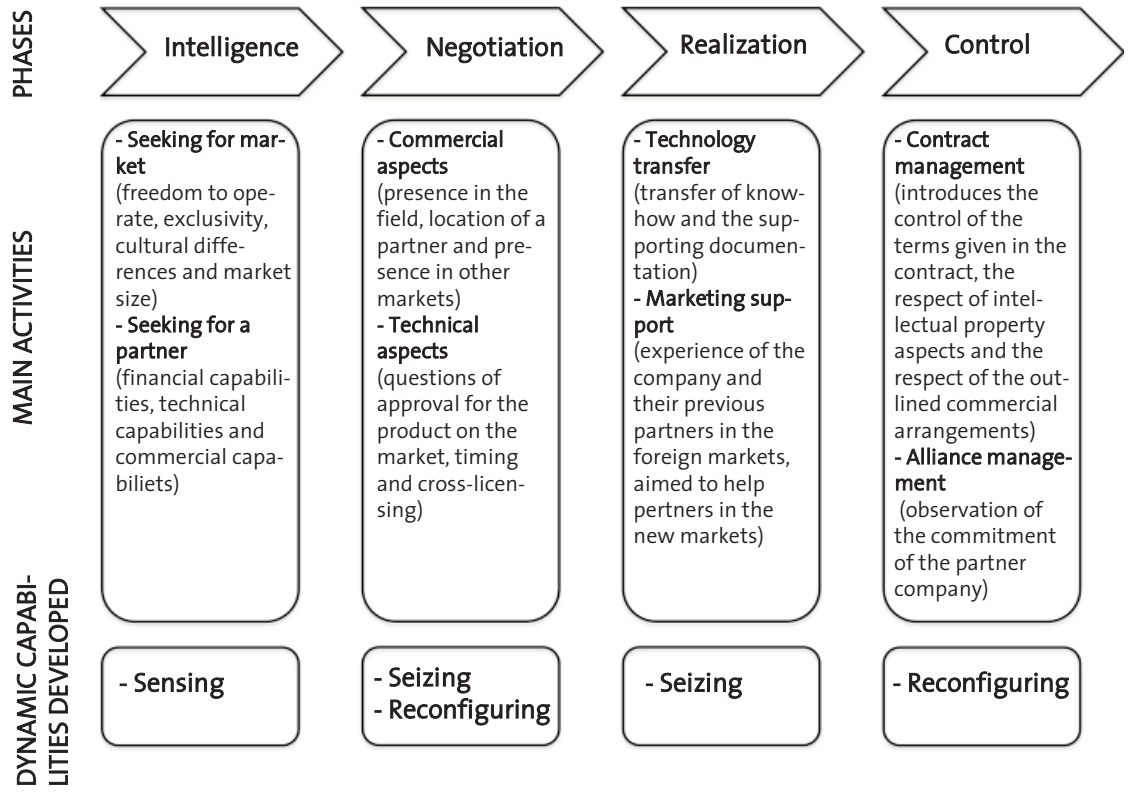
wed the formation of the reconfiguring dynamic capability. In the 75 percent of the firms some elements that improve the appropriateness matters (Galunic and Rodan, 1998), timeliness matters (Zott, 2003) and efficiency matters (Kogut and Zander, 1996) have been found. As the Head of Licensing & Business Development in Company B said, after the realization of the transfer of the technology, the firm still continues to align the partner company with the points stated in the contract. This is done with the aim to harmonize the timing and the sales amount assigned in the contract.

The Figure 2 presents proposed process of technology licensing used as the foreign market entry mode, which was developed relying on the findings from this research. In the Figure 2, the main activities in each of the phases are presented and also the dynamic capabilities which are developed along the process.

5 Conclusion

An active technology licensing has become a strategy exploited strongly within the firms. It will certainly be seriously considered in the future in the managerial research and within the companies themselves, because it enables companies to achieve both financial and strategic benefits and returns on their innovation efforts. However, the technology licensing for the foreign market entry purpose is complex and hard to manage. This paper aimed to present the process view perspective, which facilitates its management. To point out, the identified process stages may not fit ideally within the licensing as the foreign market entry mode in all the firms. Different environments and contexts of application of this process view may slightly vary, like they varied also in the firms from our sample. The papers also shows that the throughout the licensing process used as the foreign market entry mode, enables companies to develop three dynamic capabilities (sensing, seizing and reconfiguring), which are useful further on for the company. This paper, however, has not explored the performance issues resulting from the different ways of management of the licensing process as the foreign market entry mode, which is an interesting venue for the future research. As this is a quanti-

Figure 2 The process of technology licensing used as the foreign market entry mode with the main activities in each of the phases and the dynamic capabilities developed along the process.



tative based analysis, it is not appropriate for generalizing the results. In any case, the process based view can be appropriately examined by applying the longitudinal panel data analysis, quantitative research approach, which is one more suggestion for the future research.

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Appendix A

Interview Protocol

Company in general:
- Portfolio of activities, products/services
- Firm information (size, businesses, industry, location, geographical location, products and services commercialized, main financial figures)

Licensing activities:
- Technology licensing to enter foreign market (main goals, amount, frequency, people involved, reference to one or more licensing projects)
- Firms' degree of internationalization (presence in international market)

Licensing process:
- Technology licensing process identified ((i) planning; (ii) intelligence (identification and evaluation of exploitation potential); (iii) negotiation; (iv) realization (one-directional or bi-directional technology transfer); and (v) control; boundaries of each of the process stages)
- Tasks/activities in process stages (management)
- Degrees of formalization (e.g. (i) formal structures - existence of procedural routines, (ii) informal structures)

Dynamic Capabilities:
- Please indicate if the following activities appear during your licensing process used for the company to enter a foreign market (indicate also in which process stages these activities appear):
- Sensing capability:
(i) generation of market intelligence
(ii) dissemination of the market intelligence
- Seizing capability:
(i) responding to market intelligence
(ii) acquiring, assimilating, transforming, and exploiting knowledge
- Reconfiguring capability:
(i) observing appropriateness matters
(ii) observing timeliness matters
(iii) observing efficiency matters
- Please discuss how practically you perform these activities

Appendix B

Table 3 This table presents a brief description of the companies studies, their examples of licensing projects as the foreign market entry mode and describes the licensing phases identified.

Company	Company Info	Examples of licensing projects as the foreign market entry mode	Recognized licensing stages
Company A	Company A is an integrated international group that operates in life sciences sectors (diagnostics, therapeutics, instrumentation, services). - **Turnover:** over € 1 billion (65% made in foreign markets); data from 2010, data from 2011 are similar and slightly increased. - **Employees:** 3000 - **Core business:** International leader in imaging diagnostics (wide range of products and solutions for all diagnostic methods), have the biggest diagnostic centre in Italy (3-4 million analyses per year). - **Operates in:** US, Canada, Brazil, all Continental Europe, UK, Ireland, China, Japan and Scandinavia. - **Number of licensing agreements:** Not available (1500 patents, mostly to form barriers for the few breakthrough patents).	The turning point for the company was in the '80s, when the Company A developed a new breakthrough agent in radiological imaging. On one side this lead to big growth and production, but it was also a company's' decision to become truly international company, operating on a multinational basis. The Company A made a decision not only to have licensees for collecting royalties, but to establish full presence in the market. This presence was mainly through joint ventures, where Company A made a point of having a 51% of the venture (because they really wanted to have this joint venture as something on what they had control, gain direct experience from the territories and not to be seen as just a simple collector of royalties). More recently, some of the companies have become fully owned by Company A, which is their second step when entering a new market. Once the company learns how to behave, the situation is more mature to establish themselves as a fully owned company.	- **Intelligence:** Company A has alerting services that on weekly basis control patents of their interests. Alerts go through some databases which provide constant update on the given keywords and areas that the company wants to keep under control (alerted on the patent activities from other companies). When company seeks for a foreign partner, it observes portfolio of patents and their degree of specialization (potential of cross-licensing), experience of a partner, business culture of the local country (e.g. Company A managers give an example of Japan, where the employees are first loyal to the country, then to the company), location of a partner (e.g. suitable partners are in Princeton, New Jersey, where the majority of world pharmaceutical industry is based, and it is close to the university). When company wants to enter a new market it observes: **Freedom to operate** (an in-depth study of the state of the art in patents in order to check if there is a already present on that market); **Exclusivity** (how good is an exclusivity of their product: company may have the allowance to produce and sell the product, but very similar product may be available on the market). - **Negotiation:** Company A negotiates around: **commercial aspects** (financial indicators and return), **technical aspects** (approval for the product on the market and cross-licensing).

Company	Company Info	Examples of licensing projects as the foreign market entry mode	Recognized licensing stages
Company B	Company B is a family owned pharmaceutical company that is involved both in development and manufacturing of the pharmaceutical products. **- Turnover:** €68 million (10% in foreign markets); income in royalties and down payments is around 2% and it is decreasing. **- Employees:** 280 **- Core business:** Beyond the more traditional activities in the osteoarticular field and in the product pipeline renovation, tumors and the nervous system pathologies present the future areas of interest. **- Operates in:** Italy, France, UK, Canada, USA, Mexico and United Arab Emirates. **- Number of licensing agreements:** 60.	Company B licenses only finished products, so they transfer mainly the know-how, dossiers and secrets not covered by patent. Their licensing agreements are also supply agreements for the finished products. The first product from Company B today is a liquid solution for the vitamin D-3, which will probably secure the survival of the company in the next years. Company B is now searching for a partner for the authorization and distribution of the product in the main European countries. They are working hard on the life cycle management, in order to understand which new products can be created around the same molecules. On the other side, company is also improving their business intelligence activities in the other markets.	**- Intelligence:** Company B screens the companies in the market that are active in the same therapeutic field (e.g. the product for tumor they license in Canada, they explore the companies that are active only for this specific tumor), explore the real market size (by purchasing data or doing research by themselves) and cultural differences of the countries. They observe their product portfolio of the local companies, size of the company (long decision timing in larger companies may cause problems). Company B uses dedicated organized meetings, conferences or specialized fairs to contact partners. **- Negotiation:** Company B does a multiple stage negotiation. Normally, all the aspects of cooperation they combine in one agreement that includes a know-how licensing agreement, trademark license agreement and supply agreement of the finished product. **- Control:** Company B has a dedicated functional unit that works only with licensing agreements. It does not only control the **contract management**, but also an **alliance management**. This is done through periodic phone conferences and meetings, where they observe the commitment of the partner company. Company B introduces the control of yearly achievement of the minimum quantities of sales.

Company	Company Info	Examples of licensing projects as the foreign market entry mode	Recognized licensing stages
Company C	Company C is one of Italy's leading biopharmaceutical companies, with a solid history of developing innovative drugs for illnesses of high social impact. - **Turnover**: €491 million (data from 2009). - **Employees:** 800 - **Core business:** Leadership in core areas of anti-inflammatory, respiratory, rare diseases, neurology, onco/ hematology and nephrology. - **Operate in:** Italy, Germany, Belgium, Spain, Portugal, Poland, Greece, Albania, Turkey, Russia, Kazakhstan, Korea, Hong Kong, Azerbaijan, Armenia, Uzbekistan, Uzbekistan, Tajikistan, Mexico, Dominican Republic, Venezuela, Brazil, Columbia, Peru and Chile. - **Number of licensing agreements:** Not available	Company C was present in Russia, but was not satisfied with the results and wanted to change the partner. The old partner was not a local company, it was an Indian company, and it had a lot of products that were competing with Company C products. So, they found a local partner that was also able to cover the former Soviet Union countries and Eastern Europe (a regional player). The strategy was to give all the portfolio of the company to the partner. The main products in this deal are: a drug for treatment of inflammation associated with pain (the most important product of Company C) and mucolytic drug for chronic and acute respiratory diseases. Company C generally supplies with the finished product when entering a new market, because it is the way to keep it secret even when the generic production becomes available.	- **Intelligence:** Company C starts with market analysis performed by the dedicated functional unit for licensing. It has a formalized process for evaluation of potential partners, which consists of: Identification of a "Long List" of pharmaceutical companies belonging to the main National Trade Associations; Gathering of public available information relevant to assess partner's "generic and specific requirements"; Exclusion of companies with a clear business model unfit assessed through the analysis of their product portfolio and stated mission (e.g.: generic companies, specialty-R&D companies, homeopathic companies...); In depth desk analysis and profiling of short listed companies; First ranking of short listed companies based on: **Product Portfolio Fit** (therapeutic field, number of drugs, the expertise they have on the regulatory activities, presence in other markets) and **Economic and Financial Soundness** (financial foundation of the company). - **Realization:** Company C made a marketing support (the information and knowledge to enter the market) for the partnering company. It includes the Italian and foreign partners experiences. The main aim is to help them understand how the product works and which its benefits on which they should focus are. - **Control:** Partners needed to send annual marketing plan, attend meetings made to check the progress of registration and sales, send monthly reports containing sales data, comments on sales performance and information on generic products.

Company	Company Info	Examples of licensing projects as the foreign market entry mode	Recognized licensing stages
Company D	Company D is one of the leading Italian pharmaceutical groups, operates in both the pharmaceutical and the fine chemical industries. - **Turnover:** € 500 million (around 24% from foreign markets) - **Employees:** 2000 - **Core business:** Its products, all of which have a high therapeutic content, are mainly used in the cardiovascular, immuno-oncological, gynaecological, dermatological, orthopaedic and neurological areas. - **Operate in:** Italy, Russia, Brazil, Turkey, Greece, Chile, Portugal, USA, Spain, France, Morocco, Albania, Macedonia, Bulgaria, Romania, China, Korea, Vietnam, Iran, Iraq, Egypt, Libya, Algeria, Sudan, Kenya, Georgia...) - **Number of licensing agreements:** 50-60	Company D licenses the right to produce the finished product from the raw material company produces. This is their approach in Korea, Turkey and Greece. The product is the iron compound, which is their innovation breakthrough. It is iron bound with milk protein (casein). Company D has this sophisticated binding that is very tight in condition of low PH. When a patient drinks it, it goes to the stomach, where the level of PH is very low, so the biding of the protein towards the iron is very tight and no iron is released in the stomach. When this complex flows into intestine, where PH is very high, the proteins are immediately digested and iron is released and absorbed. In the common treatment of iron deficiency anaemia, one of the major side effects is the gastritis problem, especially in the pregnant women. With this product these classic iron side effects are avoided. It was released in the early 90s. In some countries there are generic producers of this compound. Company committed a lot of resources to carefully protect this compound.	- **Intelligence:** Company D looks at all the countries and finds up to 5 potential countries. Then identify all those possible partners that in these countries could bring their product to target doctors. Company observes in potential partners their structure, portfolio of products, if they had synergies with their portfolio, their sales, their presence in the field, financial capabilities, technical capabilities and commercial capabilities. These data is collected through databank, meetings, personal connections and consultants. - **Negotiation:** After identifying the partner Company D goes with the licensing deal, where they reveal: what, how, in which way and in which timing they have to do. Fundamentally, the question of time is observed. - **Realization:** It can be a transfer of know-how, or it can be even a commercial know-how. It depends on what kind of technology is transferred. If the rights for production are also transferred, the company helps the partner to produce, follows them and informs and advises them. It depends who is their partner, what kind of technology are they transferring. - **Control:** The bigger is the company, the more autonomous they are and more difficult is to follow the project. Company D follows the milestones they put in agreement and key times for the fulfilment of the tasks. Again, the point of time is more contractual than ever.

Table 4 The results of the analysis of all the process phases in order to identify the dynamic capabilities developed along the process.

Companies		Dynamic Capabilities by code							
		Sensing		Seizing		Reconfiguring			
		1.1	1.2	2.1	2.2	3.1	3.2	3.3
Company A Process Stages	P							
	I	√	√					
	N			√	√			
	R							
	C							
Company B Process Stages	P							
	I	√	√					
	N			√	√			
	R							
	C					√	√	√
Company C Process Stages	P							
	I	√	√					
	N							
	R			√	√			
	C							√
Company D Process Stages	P							
	I	√	√					
	N			√	√	√	√	√
	R			√	√			
	C						√	

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Research Paper

The Influence of the Global Crisis on the Management of the Small Firms Active in the Romanian Pharmaceutical Industry

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The recent economic and financial crisis is considered global – as it has impacted national economies, business sectors and companies. However, the impact of the crisis on a specific national economic system varies largely, case by case, both as intensity and lag time.

The purpose of this paper is to present some of the results of the research conducted in 2010 on how this global crisis has influenced the management of Romanian small and medium size enterprises (SMEs) active in the pharmaceutical sector (pharmacies) – in terms of their strategies and decisions made. The article reports some results in line with the author's previous research on firms' management and entrepreneurial spirit in Romania, bringing original elements – as decision lag time. The research methodology was survey-based, data being collected during August-September 2010.

The research offers interesting results on these companies' management. In spite of early reactions to the global crisis, a decision lag time up to two years was identified. One surprising output is that pharma SME managers – regardless of their professional and entrepreneurial skills – display a certain lack of management knowledge and culture as well as a weak understanding of what strategic management actually is. Hence, the evident outcome is that there is a need for solid management education, and training programmes in subjects like decision making and strategy.

The research conclusions are useful for both scholars and practitioners: entrepreneurs and company decision makers, as well as for management training institutions, universities and education policy makers who are participating in a life-long learning process striving to develop the managerial capacity of Romanian firms active in pharma industry.

1 Introduction

The current global financial and economic crisis began in December 2007 and sharpened in September 2008. The 'global recession of 2009' is considered by some authors as marking "the ending of a global development cycle which began in the early 1950s" (Gore 2010: 714). It has had and is continuing to have a considerable impact on different geographic regions (Jara, Moreno and Tovar 2009; Arieff, Weiss and Jones 2010; Fidrmuc and Korhonen 2010; Jha, Sugiyarto and Vargas-Silva 2010); on national economies and cross-country as well (Berkmen *et al.* 2009; Claessens *et al.* 2010; Lane and Milesi-Ferretti 2011); economic systems, business sectors, and companies. Significant research was focused on impact of the global financial crisis on different markets: equity, fixed income, foreign exchange, and emerging markets (Melvin and Taylor 2009).

The impact of this crisis varies within large limits – both as intensity and lag time (delay) – depen-

ding on how large, and powerful a national system is, how much it is connected to the global economy, and how sophisticated its banking infrastructure is. Wolf (2010) demonstrates that sophisticated finance does bring benefits (countries with larger financial sectors in '60s grew faster over the next three decades than those that did not). However, this global crisis had a softer impact on economies with less sophisticated financial products and, therefore, weaker ties with the American 'bubble' and 'toxic' financial products.

For some reasons (strong inter-links with many global firms, size of the economy) the impact of the crisis on the Romanian companies should be harder while, for other reasons (not-so-sophisticated financial products and services, government actions), softer – but delayed.

The impact of the global economic and financial crisis on Central, Eastern and South-Eastern European countries is presented by a Report of the European Central Bank, synthetically, in terms of key macro-economic indicators (Gardó and Martin 2010). As other transition economies, Romania has faced a double-shock: "a sudden stop and reversal of capital inflows, and an exports collapse due to the global slump" (Nuti 2009: 7).

It was in the summer of 2010 when the Romanian Government took action: the salaries in the public sector were cut by 25% (June 2010) and the state budget was amended (August 2010). It seems that these actions of the Government have made Romanian companies aware of the crisis rather than the company managers' own analyses and predictions (Scarlat 2011).

The pharmaceutical sector is frequently included in the chemical industry, and it is usually focused on other topics than crisis impact (mostly innovation, product development, strategy – as far as mergers & acquisitions or outsourcing). In this respect, other European countries are more attractive than Romania – as Germany (Schmidt 2011), Switzerland (Seeger, Locker and Jergen 2011), Belgium (Abrahamsen et al. 2011; Essenscia 2011; Teirlinck and Poelmans 2012) or European market as a whole (Festel and De Cleyn 2011). On the other hand, the literature on the influence of global crisis refers to the industry in general (notably, European Parliament - Policy Department Economic and Scientific Policy: *Impact of the Financial and Economic Crisis on European Industries*, Brussels, 2009) and less to the management aspects.

Consequently, the references to the management of Romanian firms facing the crisis are not rich, and the literature on the crisis impact on the management of the Romanian pharmaceutical firms is practically missing. This paper contributes to fill this gap.

The purpose of this paper is to present some results of the research conducted in 2010 on how the global financial and economic crisis has impacted the management of the Romanian small and medium size enterprises (SMEs) active in the pharmaceutical industry. The research targeted pharma SMEs from larger urban areas (cities with a population larger than 100,000 inhabitants). The focus was on the pharmacies' management and their managers' strategic and current decisions.

More specifically, the research questions were: (i) How fast the managers reacted facing the crisis; (ii) How the crisis has influenced the firm strategy; (iii) Which were the decisions made by the managers under the pressure of the crisis; (iv) How the crisis has impacted the overall performance of the firm.

The next section is dedicated to a quick but relevant literature survey.

Then the paper's structure is this: research objectives and methodology; results followed by discussion and conclusions. Some limitations are also mentioned and further research is suggested as well.

2 Theory framework

The term 'financial crisis' is applied to situations in which financial institutions lose significant part of their value, abruptly and unexpectedly. Over the last two centuries, many financial crises were associated with banking panics, crashes of stock markets, and the bursting of other financial bubbles, currency crises and sovereign defaults (Kindleberger and Aliber 2005, Laeven and Valencia 2008).

The economic crisis mechanism is intimately associated with the theory of free-market economy. The current global crisis (for direct insights see: Paulson, 2010) gave credit to Minsky's model of the credit system: Minsky (1986, 2008) stated that the free-market financial system swings between robustness and fragility (i.e. business cycle); after recession periods when companies expect profits to rise and lenders hope that the loans will be repaid – hence the risk aspect. The development is expectation- and speculation-based (Hamm 2009).

Taleb (2007) has warned the bankers about using in excess probabilistic models and missing the possibility of catastrophic events ('black swans'). The metaphor of 'black swans' is used just to define highly improbable, almost impossible to predict events. "Instead of perpetuating the illusion that we can anticipate the future, risk management should try to reduce the impact of the threats we don't understand" (Taleb *et al.* 2009: 78). More recently, Paté-Cornell (2012) re-examines the concept and adds the 'perfect storm' metaphor – to describe "the unthinkable or the extremely unlike-

ly" (as the extreme unlikely conjunction of three different regular storms: a storm that started over the US, a cold front coming from the North and the tail of a tropical storm coming from the South). Even less probably, the elements in conjunction are cause-effect linked (see Fukushima accident: Scarlat, Simion and Scarlat 2011).

The current crisis was such an unexpected black swan. Was it unavoidable? Trying to answer this question, Kaplan *et al.* (2009) emphasize the role played by the CROs (Chief Risk Officers). As the myth of the rational market is gone (Fox 2009), the 'black swan' events are behind standard deviations. The unfamiliar and difficult-to-predict events make the decision process incomparably more difficult. The crisis dynamics and predictability are investigated by more and more sophisticated mathematical models and analyses of dynamic series. Akaev (Akaev *et al.* 2010; Akaev, Fomin and Korotayev 2011) has predicted a "second wave of the global financial-economic crisis" - based on the "gold bubble" (price of gold) and prices of other commodities. Other theorists are more optimistic: the next economic crisis could be avoided (Read 2009).

The crises arise from inherent problems in the economy and, undoubtedly, their negative effects are far more destroying for the economies. On the other hand, a crisis is an opportunity in disguise (Rumelt 2009: 35): "To survive – and, eventually, to flourish – companies must learn to exploit it". There are companies and actually company managers that perceive crisis circumstances as opportunities rather than threats: they take action, restructure their companies and/or product range, and get rid of ballast: sell less productive units, discontinue less profitable products, licence less talented people, even leaving too risky markets. In pharmaceutical terms, the company illness is cured and these kinds of actions contribute to heal the economy overall; i.e. the crises have some positive effects too – if the company managers are strategically proactive and responsive.

Recent research (Gulati, Nohria and Wohlgezogen 2010) shows that 9% of companies come out of a recession stronger than ever. Even failing early and fast in order to quickly recover and have a better start during post-crisis recovery is familiar to and used by many strategists: as example, UBS AG (Union Bank of Switzerland) cut staff dramatically while recruiting young professionals in 2008; in January 2009, the bank's shares outperformed an index of European banks over the previous quarter (Economist 2009).

Hence: the importance of the responsiveness facing crisis prospective and even crisis prediction.

The current global crisis has impacted the way managers think strategically. Recent studies are focused on SMEs (small and medium-size enterprises) strategic answers to crisis, in different regions. Ho *et al.* (2010) have examined the strategies of the SMEs from Hong Kong under the 'financial tsunami'. They found ten factors as critical for a company in an uncertain financial situation.

Before the crisis, the trend was towards longer term decisions (five years or more). Foresight exercises design scenarios and strategies by sectors or regions, for time horizons of 10-15 years or even more. This crisis is having a contrary effect – five years horizon seems to be too long for strategic decisions, because of the crisis turbulences. Will the next phase of management practice continue to be the classical strategic management (five years time horizon, more or less)? Will it evolve to longer term foresight exercises and scenarios? Will it become more conservative and risk averse (like 'three-year-strategies')? Looking for answers, the opinions of the management gurus are reconsidered. Excerpted elements from Peter Drucker's previous works are brought to light by Kanter (2009): *strategic, long-term-vision is critical to leading through turbulent times.*

Finding the right strategy during and post-crisis is vital for top managers (Sull 2009, 2010; Ghemawat 2010, Gulati, Nohria and Wohlgezogen 2010). Ghemawat argues that companies – under the pressure of international trade shrinkage and the still higher pace of China and India's development – "must factor these developments into their strategies in the new decade ... the response will be to retrench and focus on home markets ... managers cannot afford to ignore the risks of pursuing a global strategy in the uncertain years ahead" (Ghemawat 2010: 56). As the range of possible futures is large and uncertainty high, the flexible strategy is preferred to rigid strategic planning: "the companies that nurture flexibility, awareness, and resiliency are more likely to survive the crisis, and even to prosper" (Bryan and Farell 2009: 24).

This crisis definitely marks a new era in strategic management – in terms of understanding the company strategy and strategic management by its managers.

Examining the SMEs strategies under crisis, and analyzing the critical factors for a company in an uncertain financial situation, Ho *et al.* (2010) have found that only two out of ten regard cost reduction.

The management is a complex process even in stationary systems; in turbulent periods its complexity increases exponentially and all the company functions are affected accordingly. Rigby, Gruver and Allen (2009) pay special attention to 'unwise cost cutting during hard times'. Quelch and Jocz (2009) offer '7 smart ways to economize on adver-

tising' as a good management reaction to consumers' strict priorities and reduced spending – a strong argument against the typical reaction of managers to cut costs.

The crises offer lessons to be learnt – not exclusively for academia: lessons from the 90's Asian crisis (Sing and Yip 2000); how to recover after a recession (Schendel, Patton and Riggs 1976; Hofer 1980; McLaughlin 1990); and how to use marketing strategies to make the company recession-resistant (Pearce and Michael 1997). "During the crisis, it is vital to gain more information ... to substantially invest in marketing and distribution, to limit abatements, and to ensure professionalism in pricing despite the turbulences of the crisis" (Schmidt 2011: 35).

Hence: the importance of the lessons learnt from previous crises and wise decisions facing current and future ones – not automatically cutting the costs of marketing research, research and development, and human resource.

The scope of this paper is not to display the history of crises or investigate their causes [political roots of the multi-facets global crises should not be under-represented; actually, "the crisis of the euro zone is a geopolitical as well as an economic event" (Mead 2012: 18)]. The paper intends to offer a picture of how SME managers from Romanian pharmaceutical industry are aware of these three major actions:

- Be proactive and *act quickly*
- In an uncertain environment and future, *act strategically*
- Facing a crisis, *act wisely* (not necessarily cutting the costs).

3 Research objectives and methodology

According to the Health Ministry, there were 6,902 pharmacies in Romania at the end of 2010, including 4,753 in urban areas (http://www.ceepharma.com).

This research targeted pharma SMEs from urban areas (population over 100,000 inhabitants). According to the Romanian law – in line with the European Union regulations – SMEs are firms with less than 250 employees. For this reason, the sample did not include the larger pharma chains. A sample of 475 pharma units was designed (10% of the total number of pharmacies in urban areas). The sample was representative as structure (number of pharma units in the sample – proportional to the city population). Then, the specific pharmacies were selected randomly and the interview operators were trained accordingly.

The research focus was on the Romanian pharmacies' management and the overall research objective was to identify the way their managers acted facing the global economic and financial crisis, and analyze the managers' strategic and current decisions. Addressing this objective, a set of specific research objectives was set (observing the three actions mentioned by the end of the previous section):

(i) How fast they reacted; is the corresponding lag time depending on the company size?

(ii) What impact the crisis had on company strategy: did it change or not? If yes, how?

(iii) Which were the most common decisions made by the managers under the pressure of the crisis; where there any mistakes made? What sort of? Is there a reason behind?

(iv) How has the crisis impacted the firm overall performance, in the managers' view?

The survey was conducted between August-September 2010, picturing a two year period (August 2008 - July 2010). The research methodology was questionnaire-based survey – questionnaire was designed to match the research objectives. It was pretested and discussed with eight business owners and managers during the first part of 2010, then reviewed, and finally administered. To get a higher rate of answers, the survey was completed as a face-to-face interview.

As an exploratory survey, there was no age discrimination among firms. Not only business owners and top managers, but also other managers or employees were invited to answer the questionnaire.

4 Research results

The rate of return was pretty high (77.5% i.e. 368 filled questionnaires out of 475 pharma units approached). For a couple of reasons (incomplete information, more than 250 employees), eleven questionnaires were rejected; finally, the data from 357 respondents were processed. The demographic features (company size) are depicted below (Table 1). The sample was not designed to be representative in terms of the structure but to have enough firms in each category – in order to characterize that group.

Table 2 presents the necessary figures for a documented answer to the first survey objective (i). Legend: sky-blue colour for microenterprises; golden – small firms; green – medium size companies.

The total number of microenterprises in Table 2 (207) is not identical to that in Table 1 (208) because one microenterprise reacted earlier than August 2008 (as early as May 2008); this was a singular and exceptional case.

The total number of small firms in Table 2 (124) is not identical to that in Table 1 (127) because two small firms did not reacted yet (by the time of survey) and one small company has stated 'do not know'.

For these reasons, the number of SMEs in Table 2 (353) totals 4 SMEs less than in Table 1 (357).

There are several notable aspects of the research results that answer to the first research question – as pictured in Figure 1. The surveyed period of two years (August 2008 – July 2010) is divided into two equal periods, each of them with distinct features.

Period I: August 2008 – July 2009

The first reactions to crisis were visible as far back as August 2008 (two microenterprises and one small firm). This was an 'early reaction' – as the following two months no reaction was reported and after other three months only (January 2009) more pharma SMEs (13) have reacted.

This *relative maximum* in January 2009 (Figure 1) means *a decision lag time of more than one year* – as far as early decisions.

Excepting January 2009, the whole period August 2008 – July 2009 depicts management/managers' passivity.

Period II: August 2009 – July 2010

During this period, the reaction of the pharma SMEs facing the crisis is stronger – meaning more active management and more decisions made by the managers. There is an oscillatory level of reaction ('up'-s and 'down'-s), over a positive trend that culminates with *an absolute maximum in March 2010* (Figure 1). This means *a decision lag time of more than one year from early decisions in January 2009, and more than two years since crisis spark, in December 2007*.

After March 2010, the reaction level decreases apparently; however, it is not clear if this decline means less reaction in reality or it is just because the survey ended by September 2010. Further research would be recommended.

To note that oscillatory appearance (alternating 'up'-s and 'down'-s) is common to both periods.

All the above apply to all pharmacy sizes, excepting the remark to the absolute maximum: it is in March 2010 for pharma microenterprises, but in January 2010 (two month earlier) for the small pharmacies, and in September 2009 (six month earlier) for the medium size ones. The data suggest this: the *smaller the company size, the slower in reaction*. This paradox (it was expected that smaller the firm, more flexible and reactive it should be) may be explained by weaker managerial skills of the managers in smaller companies. Deeper investigations might be conducted in this respect (possible correlations between the decision lag time and company age or industry).

Table 3 depicts the impact of the crisis on the company's strategic approach (second research objective).

It is surprising to note that:

- As little as 85 companies out of 357 (23.81% i.e. less than a quarter) decided that the crisis calls for extreme decisions – which is changing the company's strategy;
- Facing the global financial crisis, more than half of the pharmacies (195 which represents 54.62%) made no change in their strategies;
- There is a worrying good part of 77 firms (21.57%) that consider routine decisions as strategy change – which is a strong evidence of *lacking the elementary managerial knowledge and culture*.

Analysis by company size shows, in general, same structure across preferences for strategy change. However, the confusion is slightly more common among microenterprises (59.74% compared to 58.26%) while 'No change policy' is preferred by the medium-sized pharmacies (7.70% vs. 6.16%). Small firms display a larger availability for strategy change (38.82% vs. 35.58%).

Changes of the product range, changes in stra-

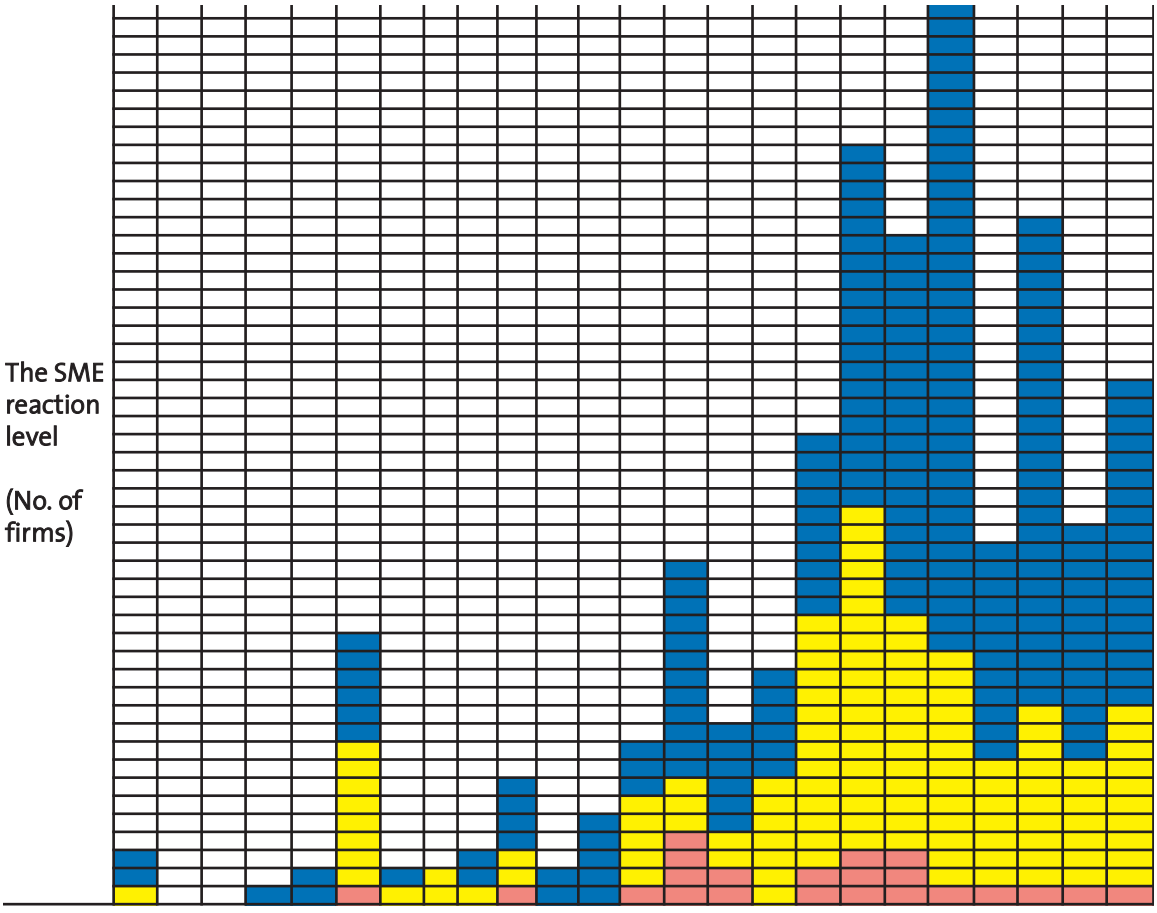
Table 1 The structure of companies by size.

Company size	Number of companies	[%]
Micro-enterprise (1 to 9 employees)	208	58.26
Small firm (10 to 49 employees)	127	35.58
Medium-size company (50 to 249 employees)	22	6.16
Total SMEs	357	100.00

Table 2 The distribution of the moments when the firm reacted to the global crisis - by size.

	Number of responding cases - by months:																							
Company size	August 2008	September	October	November	December	January 2009	February	March	April	May	June	July	August	September	October	November	December	January 2010	February	March	April	May	June	July 2010	Total SMEs
Micro-enterprises	2	-	-	1	2	5	1	-	2	3	2	5	3	12	6	6	10	20	21	36	12	27	13	18	207
small firms	1	-	-	-	-	7	1	2	1	2	-	-	5	3	2	7	14	19	13	13	7	10	7	10	124
mid-sized companies	-	-	-	-	-	1	-	-	-	1	-	-	1	4	2	-	2	3	3	1	1	1	1	1	22
Reactive SMEs	3	0	0	1	2	13	2	2	3	6	2	5	9	19	10	13	26	42	37	50	20	38	21	29	353

Figure 1 The level of pharma SME's reaction to the global financial crisis (August 2008- July 2010, corresponding to Table 2, above).



tegic alliances, retrenching are the most common strategy changes among the pharma SMEs. No case of approaching new markets was reported.

The most frequent decisions made by the managers under the pressure of the crisis (the third research objective) are presented in Table 4. More than one third of the responding firms (38.37%) made no decisions (no action facing the crisis), meaning *no responsiveness and lack of managerial abilities ultimately*.

The key results are:

- Cost cutting was the most consistent reaction of the companies facing the crisis; however, observing the sample structure, microenterprises are less inclined to do it than small pharmacies (the size of microenterprises may be a valid argument);
- Layoffs are the second-in-line decision to face the crisis; again, microenterprises are less active in making this type of decision than small pharmacies (the larger employee-base of the second category might be a good reason);
- In exchange, micro-pharmacies are more active in making other decisions – as: increasing the price (in-depth study shows about one in five – 19.05%), reducing the inventory (17.69%), product and sales promotions (11.56%);
- The medium size firms made decisions related to the range of products (less imports, new or eco-products, even cheaper products), and invested in developing the firm's identity and image;
- Other frequent decisions: renegotiation of the contracts (8.84% of all SMEs), new methods of payment (6.12%), price discounts (4.76%), freezing the salaries and hiring process (4.08%).
- Very few decisions (one or two of each type) were related to: marketing research, staff training, research in product innovation; better quality of the services provided to the clients.

The decisions made by types of costs which were cut are important too. It is encouraging to notice that cutting the administrative costs is more frequent than cutting the research-development-innovation, training and marketing costs.

The last research objective (crisis impact) is fulfilled - as the data presented in Table 5 show.

The impact of the crisis is seen in a broad display, from clearly positive to neutral to disastrous. Overall, the crisis impact is perceived as slightly negative (most of the opinions - 125). With respect to the sample structure, the microenterprises have a worse prospective (the percentage is maximum for 'disastrous' and decreases to the minimum – which corresponds to 'clearly positive' perception). The situation is exactly the opposite for the medium size companies and, more visible for the small companies (the maximum value – 73.81% - is for 'clearly positive' and falls down to only 15.38% in case of 'disastrous' future). This means that *crisis is perceived as more severe by the microenterprises*.

To conclude, the microenterprises are not only smaller but slower in reactions; they are more reluctant to take action, and have a darker prospective of the future. Their management knowledge is limited and so is their arsenal of managerial tools.

As overall result, the answer of the pharma SMEs is 'no' to all three major actions: their management/managers did not *act quickly* facing a crisis; did not *act strategically* in uncertain environment and future; did not *act wisely*, not necessarily cutting the costs.

Table 3 The changes in companies' strategies - by company size.

Company size	Strategy change		No change		Confusion *		Total	
	number	[%]	number	[%]	number	[%]	number	[%]
Micro-enterprises	48	56.47	114	58.97	46	59.74	208	58.26
Small firms	33	38.82	66	33.33	28	33.77	127	35.58
Medium-size companies	4	4.71	15	7.70	3	6.49	22	6.16
Total SME	85	100.00	195	100.00	77	100.00	357	100.00

* Confusion means that respective company manager called a routine decision as a strategic one.

5 Discussion and further research

As the Romanian financial system is not as sophisticated as the Western one, it was expected a late and not-so-devastating crisis impact. On the other hand, the SMEs are the economy's most dynamic and flexible sector, able to take the challenges (Scarlat 2003), and the links to the foreign corpo-

Table 4 The types and frequency of decisions made under the pressure of crisis - by company size.

Company size	Layoffs		Cost cutting								Other		No decision	
	Number of layoff decisions	[%]	Research Development Innovation	Training	Marketing Research & Promotion	Salaries	Administrative costs	Other costs	Total number of cost-cutting decisions	[%]	Number of decisions	[%]	Total number of „no-decision" firms	[%]
Micro-enterprises	40	51.3	7	9	6	17	26	9	74	54.4	89	60.5	90	65.7
Small companies	32	41.0	4	9	8	15	15	5	56	41.2	46	31.3	37	27.0
Medium-size firms	6	7.7	0	0	3	2	1	0	6	4.4	12	8.2	10	7.3
Total SMEs	78	100.0	11	18	17	34	42	14	136	100.0	147	100.0	137	100.0

Note: Totals do not match the total number of companies (357) - as more than one decision per company (max three) was allowed.

Table 5 The crisis impact on firms' overall performance - as perceived by their managers.

Company size	Number	The impact of the crisis is perceived as:					
	[%]	Disastrous	Clearly negative	Slightly negative	Neutral	Slightly positive	Clearly positive
Micro-enterprises	Number	22	67	79	21	13	6
	[%]	84.62	74.44	63.20	44.68	48.15	14.29
Small firms	Number	4	23	36	23	10	31
	[%]	15.38	25.56	28.80	48.94	37.04	73.81
Medium-size companies	Number	0	0	10	3	4	5
	[%]	0.00	0.00	8.00	6.38	14.81	11.90
Total SME	Number	26	90	125	47	27	42
	[%]	100.00	100.00	100.00	100.00	100.00	100.00

rations make Romanian companies more sensitive to crisis. The overall result was a delayed reaction of the firms (up-to-two-years decision lag time). The government has reacted even later (salaries in public sector cut in June 2010). It is an explanation but not an excuse for passive, inert management of the Romanian companies (Scarlat 2011). The delayed reaction of the Romanian firms, combined with the hesitations in the public sector management, lead to a longer crisis than expected; in addition to this, the current euro crisis will worsen the situation (International Monetary Fund 2012).

The survey results suggest that *smaller the company size, slower in reaction*. This is explained by weaker managerial skills of the managers in smaller companies. Deeper investigations might be conducted in this respect as well as trying to identify other possible correlations: if the corresponding decision lag time is depending – besides the company size – on industry or the company age.

The decisions made by Romanian managers show a relative small number of options – as compared to possible actions in front of a serious crisis (Ho *et al.* 2010). Reasonable interpretations might be:

- the crisis is not perceived as serious by the respective managers;
- they do not know how to answer to such threat (more likely).

Less than a quarter of surveyed SMEs decided that crisis calls for extreme decisions – which are changing the company's strategy. SMEs have shown serious lack of strategy knowledge and management culture. The proportion can easily by higher considering the possibility that 'no change policy' (195 out of 357 companies) might cover the lack of any strategy!

The impact of the crisis is seen as negative by two thirds of the pharma SMEs (241 out of 357) but the percentage is higher for microenterprises: more than four out of five (168 out of 208 which is 81%). The smallest SMEs are more sensitive, the crisis is tougher for them, and they feel the crisis impact more clearly. The lack of management culture is a key-issue within a vicious circle: no managerial tools, no/slow action; no decision, then negative impact, layoffs and cost cutting (management training included) and so on. *The crisis is more severe for the smaller but most numerous SMEs.*

Overall, the research results are positive; some answers are offered but more questions arise. A few lessons were learnt to improve the research methodology – as format of the questionnaire (more focused on management issues like decision making cycle). Most of the survey results are in line with previous research (Scarlat 2010, 2011).

A significant limitation of this research is that only urban pharma firms were surveyed. However, unless a further research will be conducted, there are arguments to assume that in rural areas the diagnosis and results will not be more optimistic.

6 Conclusions

This exploratory research aimed at identifying characteristic elements of the Romanian pharma SMEs' management, under the pressure of the crisis, by size. The results have matched the research objectives and promisingly created a foundation for further in-depth studies on correlations between firms' reaction and their performance, eventually by company size and age, region, or industry.

6.1 Late recognition and reaction

The early reactions to the global crisis were reported as early as August 2008; January 2009 marked a local maximum; reaction increased to an absolute maximum (March 2010), then decreased but kept high to the end of survey period (July 2010). A decision lag time up-to-two years was identified. There is no strong argument for setting a definite deadline for crisis impact.

The survey results demonstrate an even worse situation for microenterprises: *smaller the company size, slower in reaction* – explained by weaker managerial skills of their managers.

6.2 Lack of strategy

Less than one in four pharma SMEs (23.81%) decided to change the strategy in order to fight the crisis challenge. More than three quarters of the SMEs have no real strategy: over half of them (54.62%) made no change in their strategies and almost a quarter (21.57%) made serious confusions in terms of strategy. The most common strategies among SMEs are rather defensive: change of the product range, changes in strategic alliances, retrenching. Lack of strategy is almost equally distributed among pharma SMEs.

6.3 Lack of management knowledge and culture and skills. Management errors

The most frequent decisions made by the managers under the pressure of the crisis are personnel licensing and cost cutting as well as: price increase, lower inventory, product and sales promotions, salary freeze, contract renegotiation – following to no clear strategy or set of priorities.

There is a strong evidence of lacking the elementary managerial knowledge among pharma

SMEs as almost a quarter of the firms surveyed consider routine decisions as strategy change. The strategy confusion is more common among microenterprises; they are more flexible, willing to act and change but they lack the management arsenal and knowledge.

6.4 More severe crisis for microenterprises

The crisis impact is perceived as negative by two thirds of the pharma SMEs surveyed; however, the percentage is higher for microenterprises (more than four out of five). The smallest SMEs are more sensitive, the crisis is tougher for *them, and they feel the crisis impact more clearly. The crisis is more severe for the pharma microenterprises.*

7 Managerial implications

The major managerial implications are the lessons learnt: mastering the tools for crisis predictability; proactiveness and responsiveness; flexible strategy; avoiding cutting the costs uniformly – with little or no analysis and/or right priorities set.

Beside its importance as theoretical concept, the decision lag time (applied in case of crisis) can be used as an overall indicator of the strategic management capacity: longer the decision lag time, lower the strategic management capacity.

The research results and conclusions demonstrate that managers of the Romanian pharmaceutical SMEs display serious lack of management culture, strategy knowledge, and decision making skills. Consequently, there is an urgent need to educate and train their managers.

The vicious circle of lacking the managerial culture (slow reaction – poor decisions – negative impact on the company performance – ...,) could be broken by training programmes in management (strategy, decision making, management skills).

As the crisis impact and lack of management knowledge and skills is more profound among microenterprises, their managers (entrepreneurs) need training programmes in the same areas, with a special focus on basic principles of business management and entrepreneurship.

The research conclusions and recommendations are useful for both scholars and practitioners: entrepreneurs and company managers, as well as for management training institutions and universities, education policy makers who are striving to develop the managerial capacity of the Romanian pharma companies.

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Journal of Business Chemistry

Practitioner's Section

Development of integrated production networks using extended material flow analysis

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Integrated production networks can be very efficient in using raw materials and energies resulting in optimized cost structures. In particular in the chemical industry integrated production networks gain competitive advantage. However, the complexity of large networks makes it difficult to predict and navigate through volatile markets and to define development strategies to meet future market demands. But, by using extended material flow analysis effects of changes in production networks can be predicted. Starting with material flow analysis and extending with cost and investment analyses while using scenario techniques, an optimized configuration of the network can be identified. Therefore, extended material flow analysis supports the strategic development of the integrated production network.

1 Introduction

A recent VCI-Prognos-study funded by the "Verband der Chemischen Industrie e.V.", a German association of the chemical industry, describes the future of the chemical industry until the year 2030 (VCI-Prognos-Study, 2012). The forecast shows a growing chemical market in which industrial countries can only compete due to their highly integrated and efficient production networks, called "Verbund". While the German chemical industry reduced energy consumption by one fifth compared to 1990, the production volume increased nearly 60% in the same period due to process optimization and effects of integrated production networks. According to the study, increasing costs of raw material and energy will force the German chemical industry to further increase their resource efficiency in order to continue to be competitive on the future global market. It is expected that the German chemical industry will increase its energy consumption by only 8 % while the production value will increase by 40%. This efficiency increase is also due to a change in the product mix: While the volume of high-end chemicals will increase, resource intense products will grow slower than the overall market. But, how to adapt the production network to meet future demands? This article gives a short overview of extended material flow analysis and demonstrates in a simplified case study its application to define proper mid to long-term development strategies for integrated production networks.

2 Integrated production networks

An integrated production network contains a web of production plants cross-linked by material and energy flows (Brudermueller, 2001, Brudermueller and Langguth, 2001, Viere, 2009). The usage of co-products of single plants as raw material for other plants or as a recycle flow to upstream production units can lead to high resource productivity and it reduces the amount of waste and emissions. Also, energy flows between the production units at different enthalpy levels reduce the overall energy consumption of the network leading to high energy efficiency. Organized in an optimized manner, integrated production networks are cost effective and, therefore, deliver competitive advantages. However, the complexity of large networks makes it difficult to predict and navigate through volatile markets and to define development strategies to meet future market demands.

There is a variety of literature (e.g., Grossmann, 2005, Proud, 2007, Duggan, 2012) about the ope-

rational planning of production units focusing on short and mid-term horizon to optimize man power and machine uptime, reducing change over time, maximizing productivity and minimizing logistic traffics. Typically tools and algorithms are used for production scheduling considering production on a high detail level but in a relatively small network subarea, e.g., one production line or one chemical plant.

Tactical and strategical planning have a wider projection horizon and, in contrast to operational planning, they have to deal with more options and uncertainties. The plans are based on estimated market demands on different planning horizon of 2, 5, 10 or even more years. They should ensure to follow the business strategy by developing the production network accordingly. In order to sustain future profitability and efficiency in the network the following questions come up frequently:

- Does the existing integrated production network serve future market demands and price structures? If not, what bottlenecks must be opened, how should the network be adapted?
- How can the productivity of the overall network be increased?
- Is the production network able to follow the strategy and vision of the company?

Extended material flow analysis contributes to answering these questions. Its professional deployment supports the development of an efficient, economic, and ecological production network. During the analysis phase it

- gives a task-oriented and transparent view of complex material and energy flows and cost structures,
- detects constraints and bottlenecks,
- reveals dependancies, correlations, and inherent product mixes,
- identifies profitable operating corridors of the existing network,
- evaluates the product portfolio, and
- defines meaningful key figures.

In further investigations using scenario technique extended material flow analysis depicts improvements with clear targets and possible solutions

- to debottleneck and optimize production capabilities,
- to adapt the product portfolio corresponding to future demands,
- to increase productivity and resource efficiency, e.g., by cycle flows of intermediates, fully utilized coupled products, waste minimization, optimal energy utilization,
- to meet safety and environmental requirements, e.g., minimize inter-site transportation of hazardous materials, combined exhaust, sewage and waste treatment,
- to support business risk assessments, e.g., shutdown of plants, limited raw material availability, big drop in prices or demands (Alberti, 2001).

Overall, extended material flow analysis prepares and supports strategic decisions in order to develop further the production network of a company. In most cases the investigation results in clear project definitions with task, target, and potential benefit. In combination with estimated investment costs and expected sales numbers the payback, return on investment (ROI) and internal rate of return (IRR) can be calculated.

3 Extended material flow analysis

This approach is based on material flow analysis described in Moeller et al., 1995, and Brunner et al., 2003. A converged material and energy network model provides the basis for the cost calculation. The subsequent analysis of the model leads to adjustments in the model. It is an iterative approach to optimize the network according to the target.

Several software applications are available on the market for material flow analysis including cost analysis. Brunner and Rechberger (Brunner et al., 2003) compared several tools with the similar example including GaBi (http://www.gabi-software.com) and Umberto (http://www.umberto.de/en/). Both tools were further developed since their comparison. Umberto was recently recommended by Gartner Inc. in their "Cool Vendors for Green IT and Sustainability 2012" report (Gartner Inc., 2012). For the analysis discussed in this article Umberto was used for material flow analysis and Sankey diagrams and Microsoft Excel for additional analyses, tables, and diagrams.

3.1 Modeling of the network & boundary conditions, initial flows

Models in material flow simulation contain transitions, arrows, and places. In transitions the transformation of material and energy flows are calculated. Places represent nodes in the model which may be just connections, stocks for material and energy, or boundary conditions at system borders (input and output). The arrows define possible connections between places and transitions. The flow direction and amount will be calculated by the algorithm. Depending on the investigation, the model size and its boundary conditions may represent a subarea of a production site only or the full production network with all different sites.

The level of detail of the model is related to the target of the investigation (Bode et al., 2011). If, e.g., the task is to analyze and optimize heat exchanger networks the details of all relevant operation units

and their material and energy flows have to be modeled (e.g., reactors, vaporizers, distillation columns, condensers, dryers). In contrast, for analysis of inter-site transportation, the modeling on plant level is usually sufficient, i.e., modeling of major operation units or on plant level with main flows between the units or plants, respectively. It is strongly recommended not to overload models since a very high level of detail increases the complexity of the model significantly, that leading to convergence issues and incomprehensible results.

Typically, material flow simulation uses the approach of a Petri net to calculate the network. That is a sequential algorithm in which every transition calculates separately all possible equations depending on new inward or outward directed flows. To start the simulation initial flows have to be defined. The initial flows may represent a market pull or a push from the raw material side at the boundary of the system or defined flows within the network. Also a combination of several flows can start the calculation. In complex networks, several initial flows have to be defined in order to get the full model calculated. The algorithm starts at the transitions where the initial flows are queued. If all transitions of the network are calculated or do not change in a following run the simulation ends.

After successful calculation of the material and energy network a post algorithm starts the cost calculation with additional cost information, e.g., fix and variable costs, energy costs, allocation rules. In production networks of the chemical industry there are usually several units with by-products, i.e., more than one product is produced simultaneously in these units. The allocation of the joint costs to all products of this unit may have huge impact on the economic efficiency of final products and, therefore, must be modeled correctly (Langguth and Brudermueller, 2001, Fandel et al., 2009). As a good example, Bode et al. describe the influence of allocation rules on the economic evaluation of different process options (Bode et al., 2011).

3.2 Analysis

Typically the analysis of the model will be carried out using several methods in combination depending on the type of investigation. Methods employed commonly include the following:

- *Balance sheets* to list flows across a defined system boundary. The system can be the overall network, subareas of the network, or single units (Moeller and Rolf, 1995). Multiple variants are possible, e.g., material or energy flows and their assigned values, grouped by material, listed by arrows, etc..
- *Pareto, ABC*, or *portfolio analysis* (Daenzer et at., 1994, Lunau et al., 2008) to cluster raw material, intermediate, and product flows and to evaluate the portfolio.
- Flow and cost analysis via *Sankey diagrams* to visualize product or product group flows and their cost structures and to detect constraints, dependancies, and bottlenecks (Schmidt, 2008a&b).

3.3 Optimization

After detailed analysis of the current model, the next step is to optimize or further investigate the network according to the task. Here, scenario technique is often used in material flow analysis to modify the network and benchmark the results or to identify cause-and-effect chains. The modifications in the network vary from adjusted initial flows to structural changes by new flows, new production units, or new technology with different selectivity modeled in transitions. For risk assessments, drastic changes should be modeled, e.g., shut down of internal power plants or important operation units, shortage of raw material. After the modifications, the new scenario has to be recalculated and analyzed.

By comparing different scenarios, sensitivity and regression analysis may help to detect root causes for constraints and dependancies. Benchmarks of the scenarios are used to evaluate the different modifications revealing favorable network configurations or most economic modes of operation. Once identified, the way from the existing network to the desired configuration can also be defined by using extended material flow analysis.

A very positive side effect of using extended material flow analysis for development of integrated production networks is the identification of clear tasks and targets for following projects which are defined by the results of the analysis. With these front-end loads the project teams have a clear picture of what has to be implemented.

4 Case study Mueller- Rochow Direct Synthesis of methylchlorosilanes

The following case study is a brief and simplified example to demonstrate how extended material flow analysis can support strategic decisions in the chemical industry with the aim to adapt the integrated production network to future market demands. According to data confidentiality, the case is based on process descriptions published in "Silicones & Industry: A compendium for practical use, instruction and reference" by Andreas Tomanek (Tomanek, 1992).

The Mueller-Rochow Direct Synthesis is a copper-catalyzed reaction of chloromethane with silicon in a fluidized bed reactor. Almost all methylchlorosilanes are produced by this direct synthesis. Methylchlorosilanes are the raw materials for silicone polymers and oils, resins and organofunctional silanes (Tomanek, 1992).

Modern fluidized bed reactors have approximately 40,000t annual capacity of raw silane, a mixture of different methylchlorosilanes. The usual composition according to Tomanek (Tomanek, 1992) is shown in Table 1.

4.1 Base scenario: 85% of reactor capacity

Usually these large scale fluidized bed reactors are implemented in highly integrated production networks with voluminous cycle streams of intermediates. In figure 1, a simplified production network is shown. The transitions are shown as rectangles with an identifier starting with the letter "T", e.g., the transition T1 is the Mueller-Rochow Direct Synthesis. The places are shown as circles where green circles with a secant on the left side are input places while red circles with secants on the right are output places. Input places represent the system boundary upstream, where materials enter the system. Output places represent the outlet of the system. In this model, the output places P3, P8 and P9 represent further downstream production lines not discussed in this case. For all internal places in this simplified model, stocks are not allowed. The arrows are shown in different colors and line width. The color defines the material or material group and the width is proportional to the flow quantity. This type of flow diagram is known as Sankey diagram (Schmidt, 2008a&b). The numbers close to the arrows are the calculated mass flows in tons. All numbers discussed are rounded numbers.

In this scenario, 1,541t of raw silicon are reacting in the Mueller-Rochow Direct Synthesis (transition T1) with 5,681t of chloromethane (blue cycle stream) to a mixture of raw silanes (green arrow, 7,102t). This should represent 85% of total reactor capacity of a certain period. 120t of waste out of the Mueller-Rochow Direct Synthesis leave the model through the output place P2. In the distillation T2, the raw silane mixture will be separated and high-boiling methylchlorosilanes (approximately 2% of the mixture) will be mostly recycled with the aid of HCl and an amine catalyst to dimethyldichlorosilane. The separated products are listed in Table 2.

From the place P5, the outlet of the distillation, the different silanes are distributed to several downstream transitions:

- In the Methanolysis 1 and 2 (transitions T4 and T5) dimethyldichlorosilane and trimethylchlorosilane react with methanol forming dimethylsilandiol and trimethylsilanol, respectively, precursors for polycondensation to silicone polymers and oils. The by-product chloromethane can be recycled as reactant for the Mueller-Rochow Direct Synthesis. This very important recycle stream is represented by the blue arrow from P7 over T13 to P6 and finally to T1.
- Methyltrichlorosilane out of the distillation reacts with methanol to methyldichloromethoxysilane and HCl in the Alkoxylation (T8). Methyldichloromethoxysilane is a precursor for resins. HCl can be recycled in T12 with methanol to form chloromethane for the Mueller-Rochow Direct Synthesis and as reactant to convert high-boiling methylchlorosilanes to dimethyldichlorosilane in the distillation as described above.

Table 1 Composition of methylchlorosilanes typically produced by Mueller-Rochow Direct Synthesis (Tomanek, 1992).

Intermediate	wt-%	Precursor for
Dimethyldichlorosilane	65-85%	Silicone Polymers and Oils
Trimethylchlorosilane	2-4%	
Methyltrichlorosilane	7-18%	Silicone Resins
Methylhydrogendichlorosilane	0.5%	Organo-functional Silanes

Figure 1 Base scenario of a simplified production network.

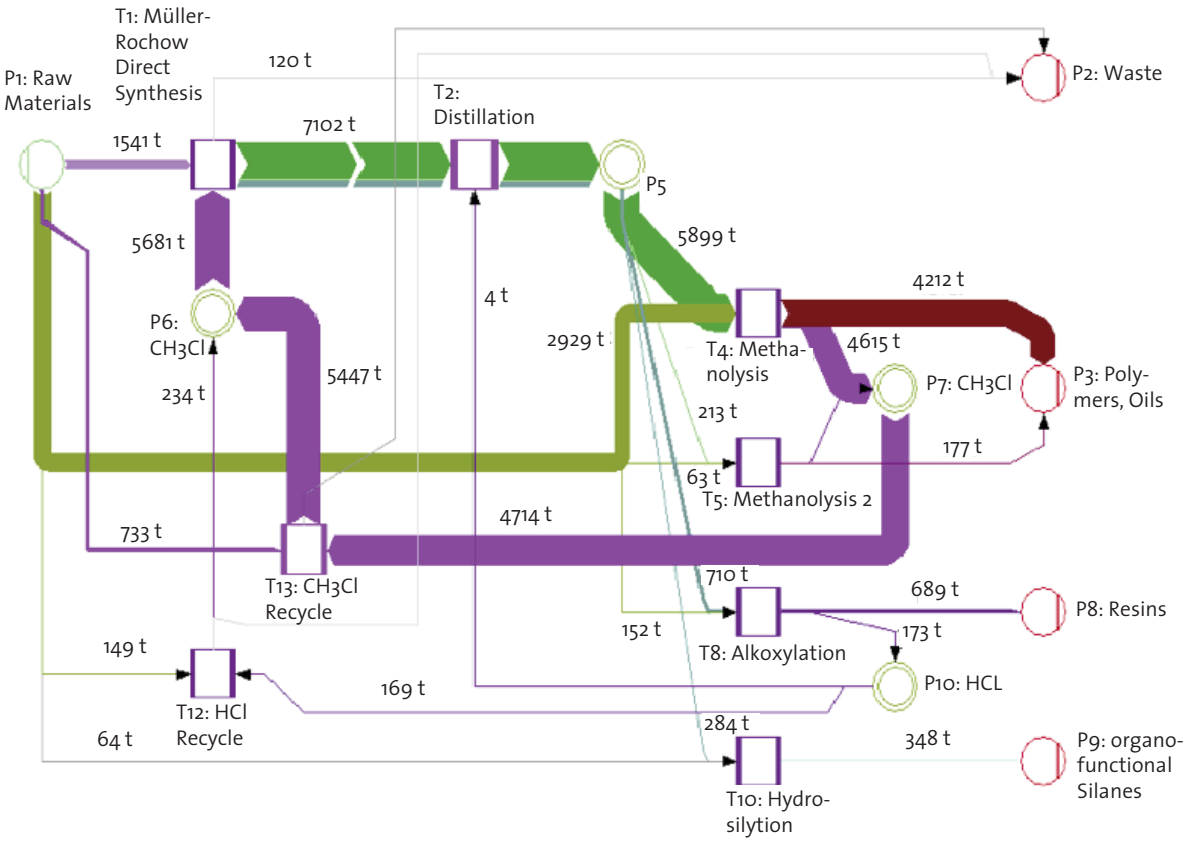


Table 2 List of intermediates after distillation.

Silane	wt-%	abs. flow
Dimethyldichlorosilane	83%	5899 t
Trimethylchlorosilane	3%	213 t
Methyltrichlorosilane	10%	710 t
Methylhydrogendichloro-silane	4%	284 t

- In the Hydrosilylation (T10) methylhydrogendichlorosilane reacts with acetylene to form vinylmethyldichlorosilane as example of numerous possible hydrosilylations to generate precursors for different organo-functional silanes.

A balance sheet over the whole network of this scenario shows that 1,541t of silicon are needed to produce 4,212t of dimethylsilandiol, 177t of trimethylsilanol, 689t of methyldichloromethoxysilane and 348t of vinylmethyldichlorosilane. Only 733t of chloromethane are from external resources while 5,681t are used in the same period in the Mueller-Rochow Direct Synthesis. About 4,615t or 81% of the required chloromethane are a by-product of Methanolysis 1 in this scenario.

In the current scenario the network produces an inherent product mix in which the output of all intermediates is fixed to a certain ratio defined by the selectivity of the Mueller-Rochow Direct Synthesis and its throughput. The market prices of raw materials and energies and the costs allocations in the Mueller-Rochow Direct Synthesis and the distillation define the internal prices of the various intermediates and finally the price of the end products of all products downstream.

4.2 Target: Adapt production network to changed market demands

In this case study, a market survey reveals higher demand on organo-functional silanes while the rest of the market remains stable. This leads to a higher demand on methylhydrogendichlorosilane as a precursor for different organo-functional silanes.

In the following sections, several scenarios will be investigated using extended material flow analysis to find the best adaption of the integrated production network in order to meet the future market demands. In a first step, several assumptions are made to simplify the study:

- enough raw materials and utilities are available
- no bottlenecks in production units, cycle streams, and downstream processes
- sufficient separating efficiency of distillations and other separation units

4.3 Scenario A: Full reactor capacity

The overall throughput of the Mueller-Rochow Direct Synthesis will be increased from 85% to 100% (1.2 times) in this scenario A. In figure 2, the Sankey diagram of this scenario is shown. As expected, all flows are increased by 1.2 times. A balance sheet of this scenario will show input flows of 1,813t of raw silicon, 3,874t of methanol and 863t of chloromethane to produce 4,956t of dimethylsilandiol, 208t of trimethylsilanol, 811t of methyldichloromethoxysilane and 410t of vinylmethyldichlorosilane.

A comparison with the base scenario discloses that an increase of only 62t precursors of organo-functional silanes is attended by a 744t increase of dimethylsilandiol, 31t increase of trimethylsilanol and 122t more methyldichloromethoxysilane. Since the market situation will not change for silicone polymers, oils, and resins these are undesired overcapacities possibly leading to price drops and lower contribution margin on these final products.

4.4 Scenario B: Full reactor capacity and adapted selectivity

In order to increase the output of methylhydrogendichlorosilane without significant change of the output of all other methylchlorosilanes the raw silane mixture must be varied. In an example published by Tomanek (Tomanek, 1992) the influence of concentrations of lead on the selectivity of the Mueller-Rochow Direct Synthesis is described (see table 3). The selectivity of dimethyldichlorosilane drops significantly with more than 50ppm lead whereas the selectivity of methyltrichlorosilane increases slightly and that of methylhydrogendichlorosilane heavily with higher lead concentration. According to Tomanek (Tomanek, 1992), lead has no influence on the selectivity of trimethylchlorosilane but results in lower Si conversion which effects on a different operation of the unit which is not considered in this study.

In this scenario, at 100% throughput of the Mueller-Rochow Direct Synthesis with adapted selectivity 4,995t of dimethyldichlorosilane are produced, 15% less than in the base scenario with only 85% throughput. Still 1.2x of trimethylchlorosilane is produced according to the higher throughput since the lead concentration has no effect on its selectivity. Significantly more amounts of methyltrichlorosilane and methylhydrogendichlorosilane are produced compared with the base scenario, 1,663t (2.3x) and 1,414t (5.0x), respectively. Also, the waste flow increases by a factor of 3.7 related to the base scenario. The Sankey diagram of this scenario is shown in figure 3.

In comparison with the base scenario (see figure 1) it shows also the changes in the precursor flows: 645t less dimethylsilandiol and 30t more trimethylsilanol are produced, the precursors for the main product group of Silicone polymers and oils, while 925t more methyldichloromethoxysilane is produced, the precursor for resins. The output of vinylmethyldichlorosilane, the target precursor for this case study, increases by 1,386t from 348t to 1,734t.

Figure 2 Sankey diagram of scenario A with 100% throughput.

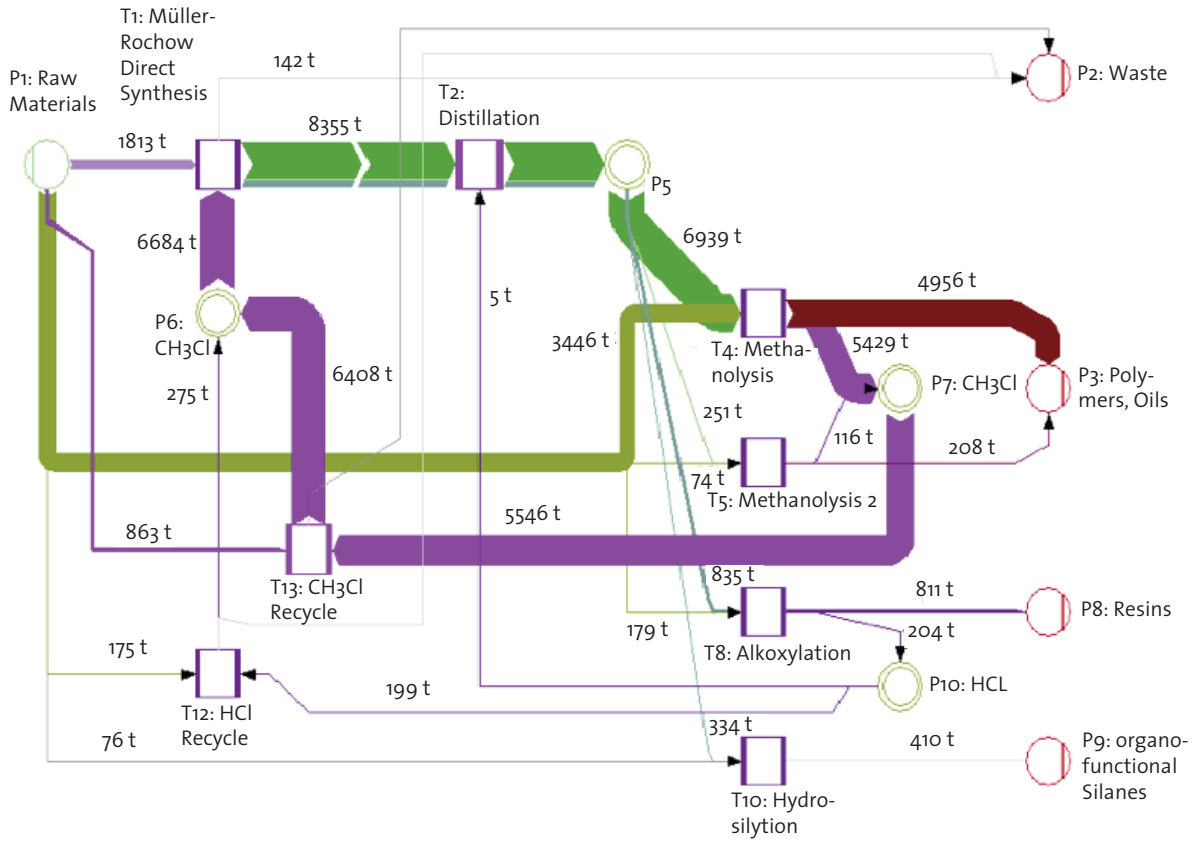


Table 3 Influence of concentrations of lead on the selectivity of the Mueller-Rochow Direct Synthesis (Tomanek, 1992).

Silane	< 5 ppm Pb	≥50 ppm Pb
Dimethyldichlorosilane	83%	60%
Trimethylchlorosilane	3%	3%
Methyltrichlorosilane	10%	20%
Methylhydrogendichloro-silane	4%	17%

According to stoichiometric, the ratio of feed stock to the reactor changes from 6,684t chloromethane (3.69 : 1) in the scenario A to 6,944t chloromethane (3.83 : 1) in the scenario B to a constant feed of 1,813t silicon. Since less dimethyldichlorosilane is produced in this scenario, less chloromethane is recycled (4,024t) and accordingly more has to be compensated by external sources (2,365t versus 863t in scenario A). Depending on the market prices of raw silicon and chloromethane, costs for waste disposal and the allocation of costs at the Mueller-Rochow Direct Synthesis and the distillation these changes will have a substantial effect on the conversion costs of intermediates and final products.

4.5 Scenario C: Full reactor capacity at adapted selectivity and converter

In scenario B the output of the main precursor for silicone polymers and oils, dimethylsilandiol, is 645t less than in the base scenario. Moreover, there is more methyldichloromethoxysilane than needed for resins. Tomanek described a process to rearrange trimethylchlorosilane and methyltrichlorosilane to dimethyldichlorosilane in presence of aluminum chloride (Tomanek, 1992). The network shown in figure 4 is extended by a converter (T3) undergoing this rearrangement. As initial flow the input to the converter is set to consume the full amount of trimethylchlorosilane out of the distillation in order to compensate the discrepancy of the throughput of dimethylsilandiol in scenario B to the base scenario as much as possible.

The mass flow of dimethyldichlorosilane to the Methanolysis 1 is due to the converter 95% of the flow in the base scenario leading to 3,990t of dimethylsilandiol for further processing to silicone polymers and oils. Since the full amount of trimethylchlorosilane and 343t methyltrichlorosilane are utilized by the converter, no trimethylchlorosilane reaches the Methanolysis 2 leading to zero trimethylsilanol. In this case, trimethylsilanol has to be purchased from external resources since specific mixtures of dimethylsilandiol and trimethylsilanol are needed to produce silicone polymers and oils. In addition, the reduction of methyltrichlorosilane feed to the Alkoxylation reduces the amount of methyldichloromethoxysilane by 333t related to scenario B without converter but still 592t more than in the base scenario. The mass flow of methylhydrogendichlorosilane is not influenced by the additional process of the converter. Therefore, the amount of vinylmethyldichlorosilane is equal to scenario B and 5.0 times higher than in the base scenario.

The higher amount of chloromethane recycled from the Methanolysis leads to 10% less external supply of chloromethane to feed the Mueller-Rochow Direct Synthesis. Depending on raw material prices, costs allocation rules, and conversion costs of the converter unit, the reduction of external supply of chloromethane may counterbalance the higher cost of the dimethyldichlorosilane due to the additional converter unit.

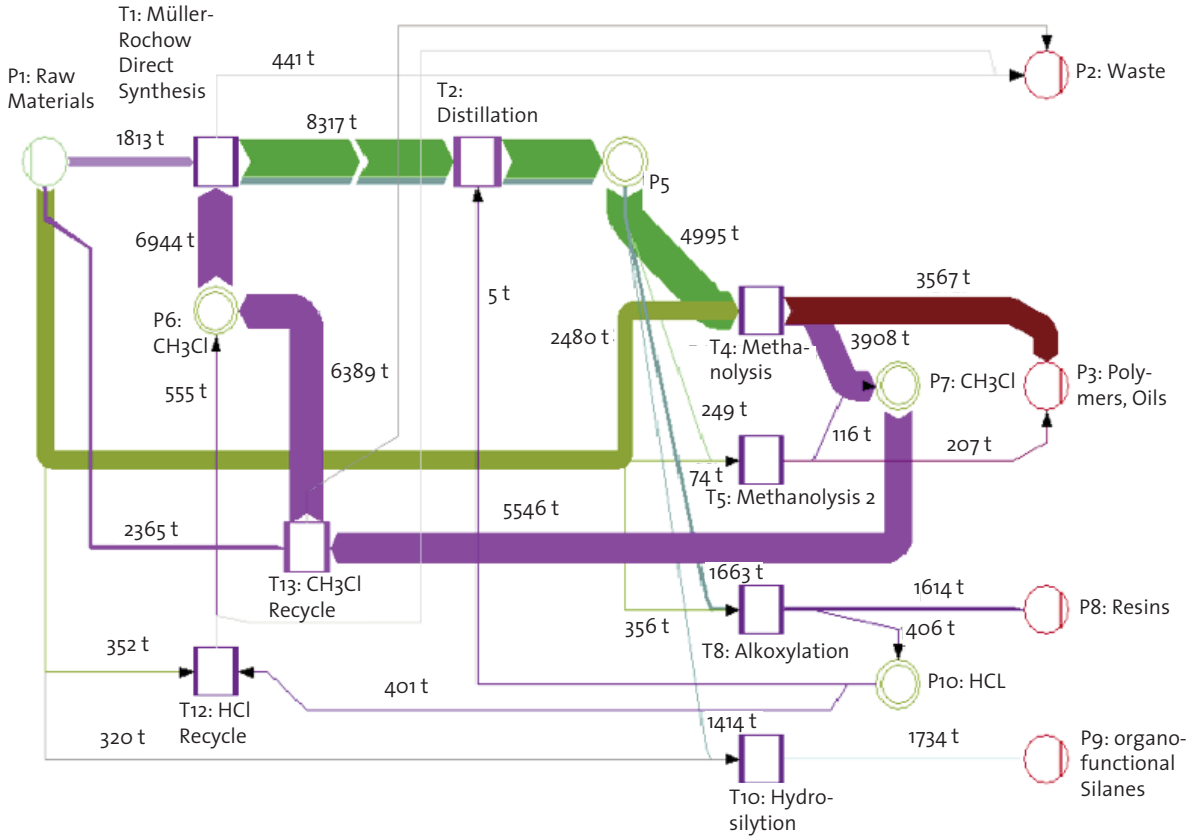
4.6 Benchmark of scenarios

The target of this case study is to find the best adaption of the integrated production network to meet the future market demand especially the higher demand on precursors of organo-functional silanes. After investigating several scenarios the results must be benchmarked. According to the target of the study the mass flows of the precursors will be compared first.

In figure 5 the mass flows of the different precursors are shown by the various scenarios. The output of vinylmethyldichlorosilane as the representative of numerous precursors of organo-functional silanes increased in every scenario compared to the base scenario. In scenario A with 100% throughput the increase is only by a factor of 1.2 while in the scenarios B and C with adapted selectivity of the Mueller-Rochow Direct Synthesis the increase is 5.0 times. There is no difference between scenario B and C because the added converter unit in the latter has no influence on the output of vinylmethyldichlorosilane. Since no specific volume of the future demand on organo-functional silanes is defined in the case study, the scenarios cannot be further assessed regarding the throughput of the organo-functional silanes.

In this case study the future demand on precursors for silicone polymers and oils and for resins remain stable. Only in scenario C the throughput of dimethylsilandiol is nearly equal to the base scenario. In scenario A the throughput is 18% or 743t higher while in scenario B the throughput decreases by 15% or 645t. Concerning trimethylsilanol the scenarios A and B are equal with 18% or 31t increase. Only in scenario C the output of trimethylsilanol drops to zero since the converter consumes all of trimethylchlorosilane to compensate the insufficient throughput of dimethylsilandiol. For further investigations the weighting between dimethylsilandiol and trimethylsilanol must be defined to optimize the converter throughput accordingly. The weighting may be defined by a combination of market demands and prices and also by the contribution margin of final products and the availability of the precursors on the market. Comparing the outlet of methyldichloromethoxysilane in the different scenarios, the mass flow is always higher

Figure 3 Sankey diagram of scenario B with 100% throughput of the Mueller-Rochow Direct Synthesis with changed selectivity by using 50ppm lead.

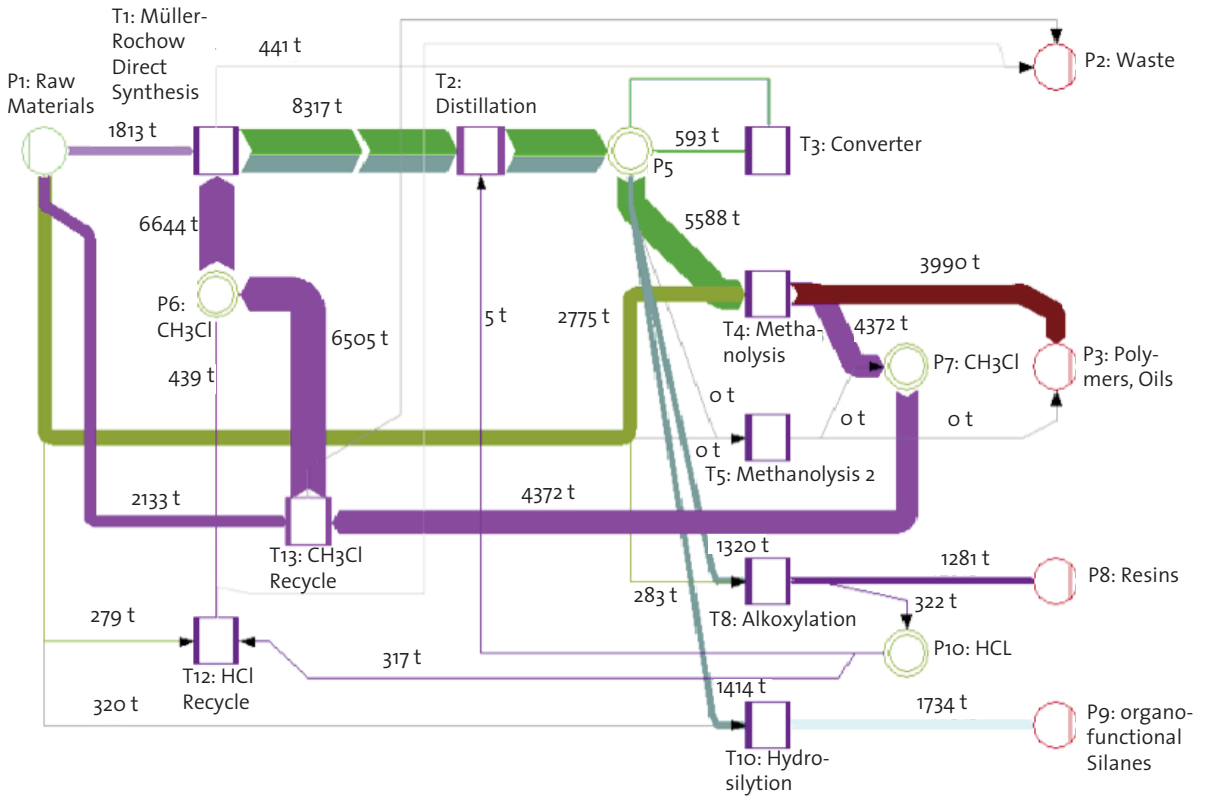


than the market demand referred to the base scenario. In scenario A and B additional 122t (1.2x) and 925t (2.3x) are produced, respectively. The high surplus production of methyldichloromethoxysilane in scenario B is reduced in scenario C by the converter unit leading to 592t or 1.9 times higher throughput relative to the base scenario.

After having discussed output flows of the network in the paragraphs above figure 6 shows the major input flows. In the scenarios only two throughput levels of the Mueller-Rochow Direct Synthesis are discussed, 85% and 100%. Accordingly only two mass flows of raw silicon are considered as initial flows, 1,541t in the base scenario and 1,813t in all other scenarios.

Chloromethane as the second reactant in the Mueller-Rochow Direct Synthesis is mostly supplied by a recycle flow from the Methanolysis units. The deficit on chloromethane must be purchased from external suppliers. The scenarios show a wide variation of external chloromethane supply. The increase of a factor of 1.2 in scenario A is only due to a higher throughput of the Mueller-Rochow Direct Synthesis while the significant increases in scenarios B and C, 3.2 times and 2.9 times, respectively, are due to the change of the selectivity. Higher amounts of methyltrichlorosilane and methylhydrogendichlorosilane are produced in the Mueller-Rochow Direct Synthesis in these scenarios and in their further processing to precursors of resins and organo-functional silanes no chloromethane is created as a by-product feeding the recycle flow. Assuming higher costs for external chloromethane supply compared to internally recycled this

Figure 4 Sankey diagram of scenario C with 100% throughput of the Mueller-Rochow Direct Synthesis with changed selectivity by using 50ppm lead and a converter to rearrange trimethylchlorosilane and methytrichlorosilane to dimethyldichlorosilane.



effects directly the cost structure of all precursors.

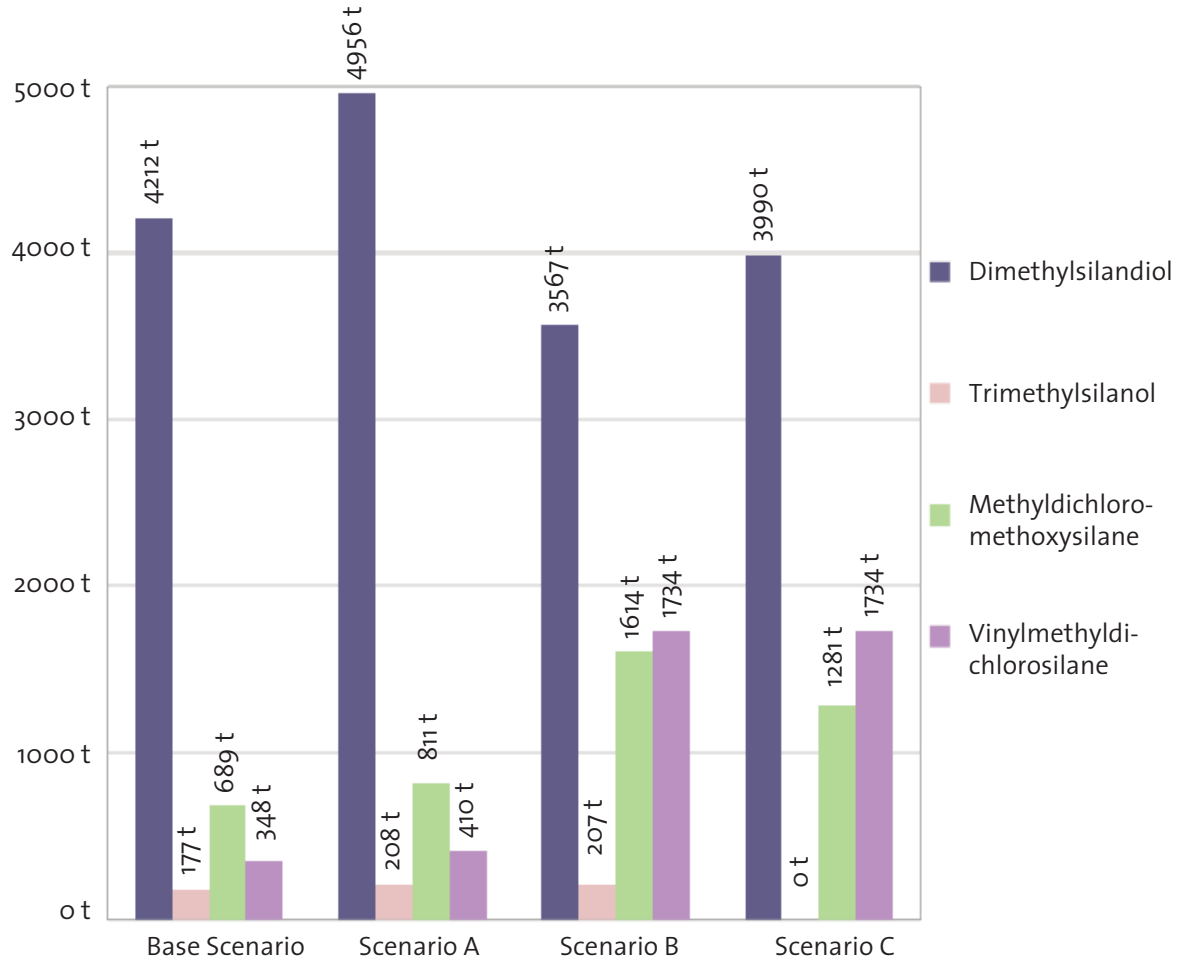
The variation of methanol supply in the different scenarios is mainly driven by the throughputs of Methanolysis 1 and Alkoxylation and its corresponding HCl-Recylce unit (T12). The demand on acetylene is directly related to the vinylmethyldichlorosilane throughput.

The benchmark should be continued with a cost analysis. Using extended material flow analysis the calculation of conversion costs and contribution margins deliver the necessary data base. Several important factors can be included in this cost analysis, e.g., fix and variable costs of all operation units and price elasticity of raw materials, utilities, energies, and final products. Especially the allocation of costs at coupled productions must be considered.

After identifying valuable scenarios from a material and cost perspective the benchmark can be extended by technical feasibility studies and investment estimations. This includes a bottleneck analysis of all operations units and material transport systems, for instance

- Mueller-Rochow Direct Synthesis,
  - capacity of crushing and mixing devices
  - fluidized bed throughput defined by residence time and thermal household
  - cyclone, filter, and scrubber limits
  - capability of compressors, pumps and evaporators, pipes and conveyors, etc.
- capacity and efficiency of distillation/separation,
  - separation efficiency on different feed stocks (pressure levels, reflux ratio, fee-

Figure 5 Mass flow of precursors in the various scenarios.



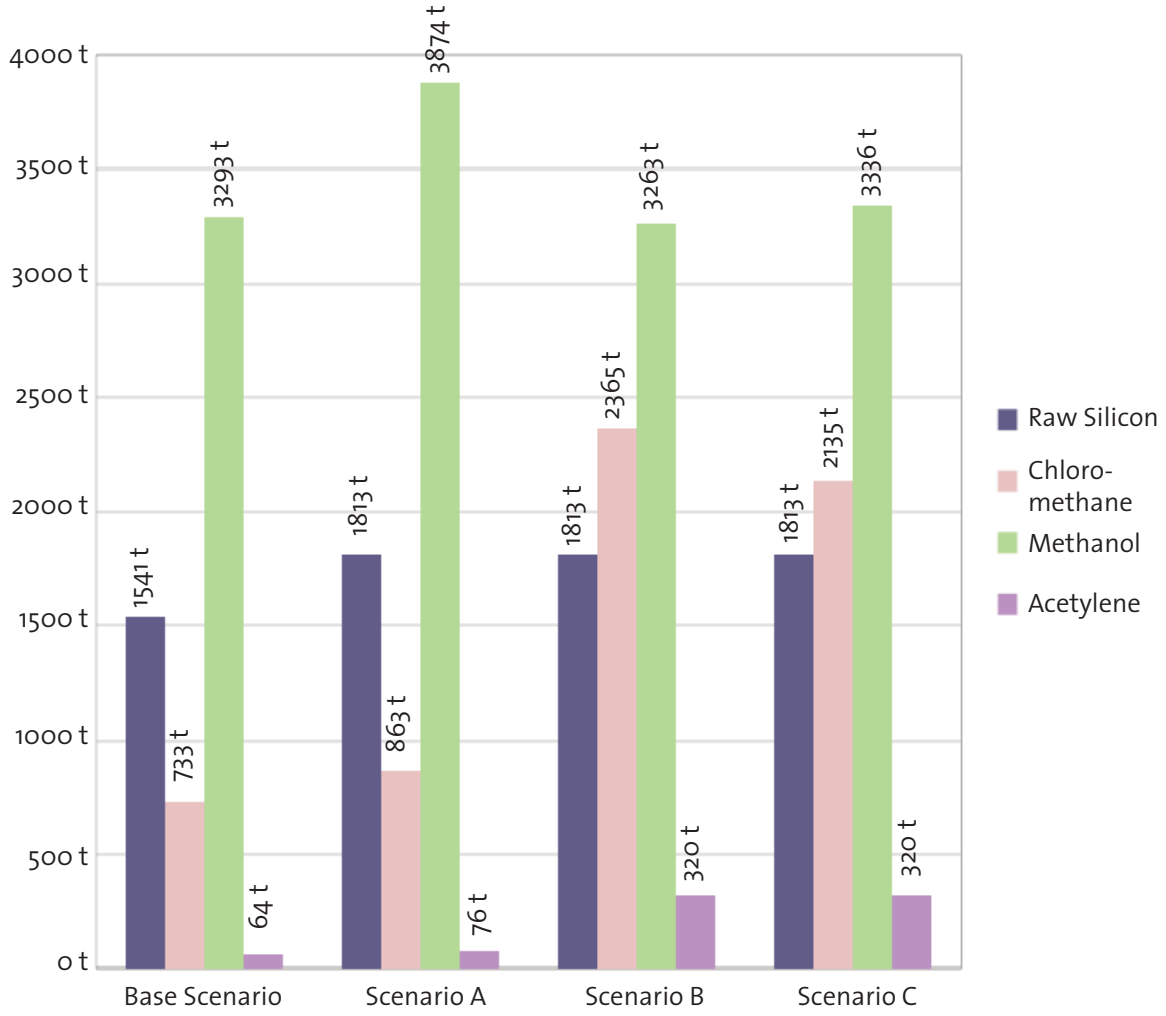
ding points, etc.)
- dimensions of columns and heat exchangers

- capacity of cycle flows,
  - transport and interim storage
  - reconditioning and treatment
- capacity of downstream units,
  - cycle times and reactor dimensions
  - capacity of post processing units, e.g., cleaning, packaging, etc.
  - operation planning of batch and semi-continuous processes
  - interim storages
- Configuration of utilities and energy suplies, e.g., heat integration via pinch technology,
- Environmental and safety matters, e.g.,limits on waste disposal or storage of hazardous materials.

Based on the bottleneck analysis the necessary investments for the debottlenecking can be estimated. Moreover a timeline and a transition plan should be developed how the current configuration of the integrated production network should be transferred into the new configuration according to the investigated scenario. It is important to consider the transition phase in the benchmark since production should continue efficiently as long as possible during the transition which typically takes several years. Not all scenarios will have the possibility to earn money during the transition into the new configuration. The transition phase can be modeled stepwise using several extended material flow analyses.

Important key figures can be estimated using the collected data of every scenario and benchmarked, e.g., ROI , IRR, earnings before interest, taxes,

Figure 6 Mass flow of raw materials in the various scenarios.



depreciation and amortization (EBITDA), etc..

A full benchmark can be done using a weighted decision matrix where every scenario is scored along a set of criteria or key figures (Grundig, 2006, Lunau et al., 2008). The weighting factor of every criterion or key figure is multiplied with the score and summed up to a total score per scenario. The highest total score is the best scenario according to the criteria and weighting. The extended material flow analysis is an iterative process. Any target conflicts depicted in the benchmark may lead to ideas or combinations of new promising scenarios which shall be investigated.

5 Discussion

In a simplified case study the methodology of the extended material flow analysis is demonstrated. Even if the discussed drastic change in the product mix due to a change in the selectivity of the Mueller-Rochow Direct Synthesis cannot be produced without huge investments in different production lines, it demonstrates the strong effect of few process steps on the product portfolio and on the economic efficiency of an integrated production network. It also demonstrates the complexity and sometimes unexpected results of changes in these networks. Especially the conversion cost of the final products in an adapted network estimated by cost analysis is of high value for far-reaching decisions. In the discussed case further literature search may reveal an adapted change of the selectivity of the Mueller-Rochow Direct Synthesis to better fit to the market demands and reduce investments. Extended material flow analysis can be also used here to define the target for a R&D project to

identify specific process conditions of the Mueller-Rochow Direct Synthesis to adjust the selectivity according to the defined optimized scenario.

Starting with material flow analysis and extending with cost and investment analyses while using scenario techniques, an optimized configuration of the integrated production network can be found by using extended material flow analysis. The potential to consider the majority of relevant aspects describing the capability and efficiency of integrated production networks makes this methodology very powerful and beneficial. One modeled network can be analyzed from different perspectives simultaneously, e.g., resource efficiency and productivity, economic and ecological efficiency, life cycle assessment (LCA), technical capability, and risk assessment.

The descriptive and prescriptive character of the extended material flow analysis allows estimation of unknown flows, identification of constrains and correlations, cause-and-effect chains, dependancies between throughput, energy consumption, and costs providing a basis for product and project portfolio analyses, profitability analyses, and investment appraisals, to name only a view possible applications of extended material flow analysis. Using various display formats, e.g., balance sheets and Sankey diagrams, even complex results of an investigation can be presented in a transparent and comprehensive manner. Therefore, extended material flow analysis supports the definition of proper mid to long-term development strategies for integrated production networks to follow the company's vision.

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Journal of Business Chemistry

Practitioner's Section

Personalised medicine, unmet need or business strategy?

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Personalised medicine is a discipline that integrates pharmaceutical development with existing knowledge about the genetic and phenotypic factors that influence drug response. This integration enables tailoring therapies to individual patient's characteristics to help improve their safety and efficacy. Personalised medicine implies a shift in the way drugs are delivered as it requires new forms of testing that assess the patient´s eligibility for a drug. This poses new challenges, both at a regulatory and reimbursement level.

Personalised medicine has reached higher commercial success and clinical uptake in drugs under development than old and off-patent drugs. This paper uses the case of TPMT testing to illustrate the reasons why personalised medicine for off-patent drugs is less used at a clinical level than personalised medicine for drugs under development.

1 Introduction

Personalised medicine (PM) is new approach to health care. It focuses on the study of the differences in drug response among group of individuals who share common genetic or phenotypic characteristics (Lindpaintner, 2003).

PM has improved the understanding of disease and drug response and is enabling better approaches to target discovery and drug development (Shah, 2004). Response to drugs has a genetic and/or phenotypic component and genetic and/or phenotypic variations among groups of individuals determine how they respond to drugs (Evans and Johnson, 2001). These differences are identified through biomarkers that (when transformed into companion diagnostics) have the potential of improving the safety and efficacy of both licensed drugs (blockbuster drugs) and drugs under development (minibuster drugs) (Lewis, 2003, Webster et al., 2004). For this, PM has been defined by two technological trajectories illustrated in figure 1). The first one focuses on safety, the second on efficacy (Hedgecoe and Martin, 2003).

However, despite the promises around PM, few companion diagnostics have been launched to the market, most of these directed to drugs under development (i.e. Gleevec® in Philadelphia chromosome-positive chronic myelogenous leukemia, Herceptin® in HER2-positive breast cancer or Iressa™ and Tarceva™ in EGFR-positive lung cancer). Until now, the pharmaceutical industry has been more focused in the use of PM to drugs that are being developed rather than to drugs which are 10-50 years old (Human Genetics Commission, 2002).

Pharmaceutical companies urge to find strategies to face the decrease in the number of chemical entities to market. Despite the increase in research and development budgets over the last decade, the drug industry has been suffering a decrease in the number of marketing applications and approvals (Arnold and Hall, 2005). An increasing number of failures during regulatory approval, problems in the characterizing drug-dose effects and difficulties in measuring the risk-benefit ratio of new drugs have been at the origin of the problem (Di Masi et al., 2003). The increasing number of failures during regulatory approval, problems characterising drug-dose effects and difficulties measuring the risks benefit ratio of new drugs have accelerated the decrease of chemical entities to market (Di Masi et al., 2003). In addition, the constraints on clinical development due to a higher burden from regulators, the need to develop complex products with longer clinical development processes to ensure effectiveness in chronic patients

and special sub-populations, and the need to carry these trials globally were some of the additional barriers in drug development (Milne, 2002).

Any new medicinal compound entering Phase I clinical trials have only an estimated 8% chance of reaching the market (FDA, 2004) and, even after approval, drugs may be withdrawn because of safety concerns. From 1990 to 2006, 38 drugs were withdrawn from major markets due to safety problems (Shah, 2006). Between 1998 and 2002 the average annual number of new drugs approved by the FDA was 68, by 2003, this number had dropped by two-thirds. In 2004 the number of approved drugs was 21 (Need et al., 2005).

2 Scope, research questions and hypothesis

This paper analyses, retrospectively, the technological trajectory of TPMT testing and the process of clinical uptake by the UK National Health Service (NHS) until 2009. The purpose of the TPMT case study is analysing the main enablers and barriers during the introduction of TPMT testing in the NHS as well as the major hurdles associated to the process of reimbursement. In particular, the paper addresses the following questions:

- What were the main drivers and barriers that facilitated and/or hindered the use of TPMT testing in the NHS?
- How have these drivers and barriers shaped the process of technology diffusion?

These questions are answered assuming the following hypothesis:

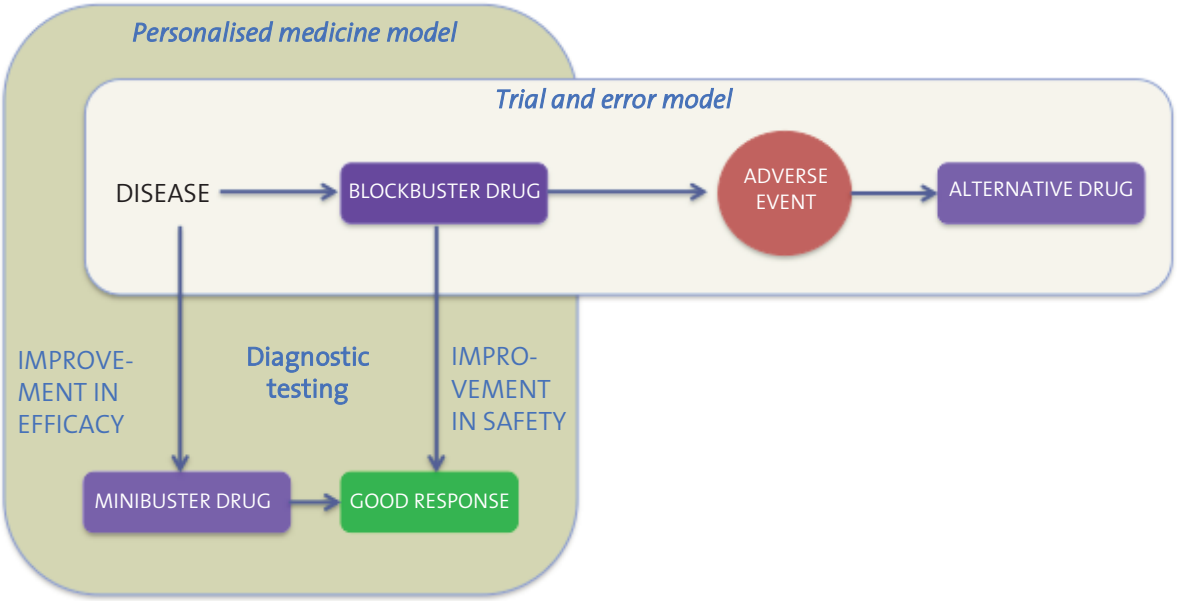
- The use of companion diagnostics or pharmacodiagnostics for improving the safety of off-patent drugs in the UK is less formalised than the use of companion diagnostics to improve the efficacy of drugs under development, because the reimbursement system for pharmacodiagnostics in the UK, is not designed to evaluate the unmet need of diagnostic or pharmacodiagnostics tests but their business potential.

3 Conceptual Framework

The conceptual framework used in this case study lies in three bodies of literature: diffusion of innovations theory and user-producer interactions to explain the process of technological diffusion and, socio-technical systems to explain the context of the diffusion.

3.1 Diffusion of innovations theory

Figure 1 Shift from a trial and error model of drug prescription to a personalised form of drug use to improve either safety or efficacy.



The adoption and implementation of innovation has been traditionally explained through concepts addressed in the diffusion of innovation literature, which classical approach was developed by Rogers (Rogers, 1962). This model understands diffusion as the spread of ideas, mainly by imitation, with a special emphasis on the influence of social networks and how opinion leaders and individuals take adoption decisions. This concept stands on five principles: (1) the degree to which the innovation is perceived as being better than the previous one (relative advantage); for instance whether it represents an advantage in effectiveness and cost-effectiveness; (2) the extent to which it is perceived as being consistent with the existing values, professional norms and ways of working (compatibility); (3) the complexity of the innovation, the barriers that need to be overcome and its difficulty of being used; (4) the possibility of experimenting with the innovation (trialability) and (5) the degree to which its results are visible to the intended adopters (observability). Innovation would be more easily adopted if the potential adopters could adapt and modify (or "reinvent") the innovation to suit their own needs and innovations would be more rapidly "diffused" the more they complied with these principles.

This model was adapted by medical sociologists to explain the introduction of tetracycline in clinical practice (Coleman et al., 1966). However, Rogers' five step unidirectional rule is not applicable to medical innovation for various reasons.

- The diffusion of medical technologies involves a variety of actors and institutions, who need to align their differing interests through a process of collective social learning that will lead to the acceptance of certain technological trajectories and the rejections of others (Dosi, 1982).
- Technological change in medicine relies on a series of feedback mechanisms among users and producers, who engage in a series of interactions that contribute to the re-shaping of the innovation (Gelijns and Rosenberg, 1994). In addition, medical innovation is highly regulated, both at the point of development and delivery and these regulations are also involved in these feedback mechanisms.
- According to Rogers, consumers are the final users of the innovation. However, in the case of medical innovation, clinicians are often the gatekeepers of treatments and, in effect, the final users.

3.2 User- Producer Interactions

While evolutionary economics and business studies focus on the production-side and the creation of knowledge and innovation, with less attention to the user side, innovation studies focus their attention on the co-evolution of technologies and markets (Coombs et al., 2001). The adoption of medical technology is neither a passive nor a unidirectional. The diffusion of technological innovation responds to a series of interactions and feedback mechanisms between the users and the developers of a technology, with the demand and supply forces determining these feedback processes (Gelijns and Rosenberg, 1994).

Von Hippel proposed that innovation processes are distributed across users, manufacturers, suppliers and others, highlighting the importance of shifting from manufacturers-as-innovators into user-producer interactions as a source of innovation (Von Hippel, 1988). According to Von Hippel, these user-producer interactions control the survival of new technological artefacts in the market and ensure a demand for them (Von Hippel, 2005).

In medicine, these user-producer interactions often take place among clinicians who prescribe drugs to patients, patients who may report adverse events to clinicians, clinicians feeding this information to regulatory agencies and regulatory agencies or pharmacodiagnostics informing the manufacturers about safety and suspected adverse events.

3.3 Socio- technical systems

The diffusion of medical innovations is socially constructed and continuously negotiated between the members of the organisation (Greenhalgh, 2005). Medical innovations are embedded in a complex socio-economic environment formed by health organisations, institutions, regulations, communities of practitioners or patient organisations. This network explains how technology emerges, develops and translates into the clinic. This implies a co-evolution and a co-shaping of the technical as well as the socio-economic (Bijker and Law, 1992), therefore, any new medical technology will only reach the clinic when the complex elements that form its socio-technical network are such that enables the translation.

For the purpose of this study we considered that TPMT testing formed a socio-technical system composed of actors with different technological views and positions about the technology. These actors include researchers, clinicians, regulators, private companies, patient groups and policy-makers.

The core of this case study lies in understanding the evolution of the socio-technical network defined by TPMT testing.

4 Methods

The methods used in this case study were aimed at gathering arguments and opinions for and against the use of TPMT testing in order to inform its technological trajectory. The research methods were qualitative and were divided in two phases, first secondary research (document analysis) followed by observational research and interviews (primary research).

4.1 Document Analysis

A first exploratory document search gathered technical information on TPMT testing. The sources of evidence consulted were biological and medical journals, published socio-economic studies, reports, product brochures, newspaper articles and unpublished work. The desk research was also intended to look for secondary data that could support the information obtained, at a later stage during the interview process. Secondary data was obtained from government publications, regulations, clinical trial protocols and patents. All these documents provided empirical information about TPMT testing and illustrated ongoing debates around the use of the test.

4.2 Semi- Structured Interviews

The aim of the interview process was (1) validating the desk research and (2) obtaining views from key informants that provided reliable opinion about the benefits and hurdles of introducing TPMT testing in clinical practice. Interviewees were first selected from the literature and then followed a snowball sampling process where each interviewee appointed other experts.

Interviewees were clustered into groups of experts: researchers (formed by geneticists, biochemists, pharmacologists, medical researchers, health economists and sociologists), clinicians (haematologists, oncologists, gastroenterologists and rheumatologists) and regulators. Interviews were tailored to each of these groups of experts. A total of sixteen interviews was undertaken. Seven interviewees were life science researchers, all of them involved in TPMT testing, in either research only or research and service provision (in the case of NHS laboratories). Three were social science researchers with expertise in TPMT testing, four were clinicinas (one rheumatologist, two haematologists and a gastroenterologist) and another four were experts in personalised medicine not specific to TPMT testing. One commercial company involved in a test (not related to TPMT testing) was also interviewed as well as two respondents with a regulatory affiliation. These were involved in regulating pharmaceuticals and, although they had extensive knowledge about PM, they were not directly involved in the TPMT testing case.

A patient organisation did not agree for an interview as it considered PM was not relevant for them. Three other patient organisations did not respond.

5 TPMT Testing in the UK

TPMT testing is a pharmacodiagnostic tool that determines the levels of the enzyme Thiopurine Methyltransferase (TPMT) in the blood. This test predicts the likelihood of experiencing a serious or very serious adverse event to the thiopurine drugs azathioprine and 6-mercaptopurine, both off patent.

Thiopurines (Azathioprine-Imuran® and 6-Mercaptopurine-Purinethol®) are immunosuppressants used, since they were first marketed in the late 1950s by Wellcome (later on Glaxo and now GSK), for treating patients undergoing organ transplant surgery. Although these drugs were firstly aimed at avoiding transplant rejection, they were later on used to treat autoimmune conditions, mainly in dermatology (dermatomyositis, pemphigus vulgaris), rheumatology (systemic lupus erythematosus) and gastroenterology (Chron's Disease, Ulcerative Cholitis), as well as in haematology to treat acute lymphoblastic leukaemia. Thiopurines, as well as any other drugs, have associated side-effects, principally a reduction in the production of blood cells that can seriously compromise the patient's health. As a consequence, patients treated with these drugs need to be closely monitored (full blood count, liver function tests and electrolyte analysis) on a weekly basis, until the treatment is stabilised.

Some of the adverse events caused by thiopurines have been associated with low levels of or the lack of the enzyme Thiopurine Methyltransferase (TPMT) (Black et al., 1998, Arenas et al., 2006). According to the levels of the enzyme in the blood, patients can be advised not to take the drug or be prescribed a lower dose; however, the response to azathioprine has also a genetic component and, mutations in the gene that codes for the TPMT gene can also be associated with adverse events (Coulthard et al., 2004, Coulthard and Hogarth, 2005, Arenas et al., 2006). However, the correlation between enzyme levels (phenotype) and mutations (genotype) is not fully understood and testing for the enzyme levels is more effective in most cases than looking for genetic mutations. Only some of the mutations implicated in drug response are known.

For ALL the situation was different. TPMT testing was part of a clinical trial ALL, where every child diagnosed with ALL underwent TPMT testing.

The major benefit of TPMT testing (phenotypic test) is diagnosing who is at risk of a severe ADR, which may be fatal. It is estimated that only 0.3% of the population might be exposed to that level of risk, 10% of the population might be at a moderate risk (not as severe) and the remaining 90% may develop a normal drug response. In the UK there are two NHS reference laboratories that offer TPMT testing although the test is not extended across the clinical community (Farguer et al., 2006). There are various reasons for this:

- TPMT testing in the UK is a laboratory developed or home-brew test. It is not a commercial kit as it does not comply with the In Vitro Diagnostics (IVD) Directive that rules the marketing of commercial diagnostic tests. On the contrary, it is a non-commercial test developed by NHS laboratories.
- The National Institute of Clinical Excellence (NICE), who is the main reimbursement body in the UK and decides which drugs and technologies should be adopted by the NHS, has not appraised the test. As a consequence, TPMT testing is not reimbursed at a central level. Individual primary care consortia (former Primary Care Trusts) may reimburse TPMT testing at a local level if they consider testing useful and necessary.
- In the lack of a formal evaluation of the test, there are different patterns of uptake between dermatologists, rheumatologists, gastroenterologists and haematologists (Payne et al., 2007). The British Society of Dermatologists considers that TPMT testing should be considered before prescribing azathioprine (Anstey et al., 2004), the British Society of Rheumatology has also adhered to this recommendation (Payne et al., 2007); however, the British Society of Gastroenterologists does not recommend TPMT testing as it considers that azathioprine has been widely used in Ulcerative Colitis and Crohn's Disease and has proved to be safe (Teml et al., 2007).

6 TPMT testing in the UK Reimbursement System

The translation of any drug or medical technology into clinical practice requires a demonstration of comparative safety, efficacy and cost-effectiveness, together with other factors like disease severity as well as other ethical, social and legal implications (Shah, 2004).

In the UK, NICE is the official body that decides on reimbursement at a national level. NICE evaluates primarily drugs but, since 2009 it also started evaluating diagnostics. NICE has a pragmatic view on how its decisions should be made and only recommends treatments below the threshold of £30,000 per Quality-Adjusted-Life Years (QALY).

TPMT testing emerged as a tool to predict adverse events originated by two off-patent drugs: AZA and 6-MP. Both AZA and 6-MP are reimbursed by the NHS because both drugs had been used before NICE started appraising technologies and because both are off-patent and therefore cheap drugs. The drugs cost approximately £20 a month (data provided by clinicians in 2007. The 2013 BNF cost of a pack of 28 pills of 25 mg is £6.02 .), while the test, £27 per patient (costs for 2007). But despite AZA is reimbursed by the NHS, TPMT testing is not, because NICE has not appraised the test and, without a "stamp" of approval that assures clinical utility, it is difficult for the NHS to justify reimbursement. Nevertheless and, despite TPMT was not appraised by NICE, the two National Reference Laboratories (at Birmingham City Hospital and Guy´s Hospital in London) offer TPMT testing to the NHS since 2003. As a result, some hospitals reimburse the test locally, depending on the cash balance of the NHE Trust or hospital as well as on other factors such as the clinician's willingness to prescribe the test or their proximity or connections with the testing laboratory.

6.1 Service Delivery

Once a TPMT test is requested by a clinician, the patient signs a consent form and a sample is sent to one of the reference laboratories. The laboratory sends a report back within 6 working days, with a narrative interpretation, in which they assign a high or low risk of myelotoxicity and warn of the need for cautious use of AZA or 6-MP, although the report is only a recommendation. Depending of the levels of TPMT in blood, patients can be classified as:

- Low risk: the patient is normal (his/her TPMT levels are normal or even higher than normal)
- Higher risk than normal (TPMT levels are low) and azathioprine should be taken with caution (clinicians often reduce the dose by half).
- High risk (levels of TPMT are very low or non-existent) and should not be given azathioprine.

Clinical demand varies across specialties. During the first year of service, referrals to Birmigham City Hospital came from the following clinical specialties: gastroenterology (66.7%), dermatology (13.6%), rheumatology (12%) and other specialties (7.7%) (Graham et al., 2004), with demand increasing in the following years. By diseases treated, TPMT tes-

ting was requested in patients with Crohn's Disease (27.5%), Ulcerative Colitis (31.9%), Inflammatory Bowel Disease (4.8%), Systemic Lupus Erythematosus (4.4%), Dermatitis/Eczema (7.2%), Bullous Pemphigoid (6.3%) and others (7.6%) (Graham et al., 2004). It should be noted here that the high demand in gastroenterology is due to the high volume of patients in this specialty taking azathioprine, which outweighs the lack of recommendation for testing in gastroenterology.

7 Drivers for TPMT testing uptake

The main factors influencing testing uptake are the following:

- Promoters of TPMT testing argue that, the benefits of testing are substantial, not only for patients who have low or no TPMT levels and should not be taking the drug, but also for people with intermediate levels, who could benefit from a reduction in the AZA dose.
- The reference laboratories suggest that TPMT testing is cost-effective on the basis that it prevents serious AEs, which treatment costs are very high. Some studies have shown that TPMT enzyme test is also cost-effective in certain situations (Payne et al., 2009, Graham et al., 2004, Gurwitz et al., 2009).
- Some clinical groups have recommended TPMT testing. The British Association of Dermatology was the first group to recommended testing, as a result, all dermatologists across the UK now refer their patients for a test before prescribing AZA (Anstey et al., 2004). Subsequently, the British Society of Rheumatologists also included TPMT testing as an option to patients on AZA. As a result, the demand for test increased among rheumatologists (Payne et al., 2007).
- In 2007, some hospitals in the UK (approximately 20 NHS Trusts) have established TPMT prescreening policies, meaning that they have implemented TPMT testing and cover the cost of testing.
- Some respondents believe TPMT testing may prevent bone marrow failure in ALL patients, particularly when routine blood tests could not detect it.
- Phenotyping or measuring TPMT enzyme levels in blood appears to be the best form of testing. The enzyme assay gives more information than the genetic assay, which only looks at the most common polymorphisms that affect drug response. But not all polymorphisms that influence drug response are known and even if they were, doing a genetic analysis of all of them would be too costly and too lengthy. For this reason, genotyping is an option, only when phenotyping does not give a conclusive indication.

8 Barriers for TPMT testing uptake

Even though TPMT testing is already available at the NHS, there are a number of reasons why the diffusion of the test is slow and remains, in some instances controversial:

- The clinical opinions about testing are contradictory. While some haematologists consider the test effective and necessary, others believe that TPMT testing would not replace routine blood monitoring and electrolyte analysis.
- Not all clinical associations believe the test has an additional benefit. The British Society of Gastroenterology has never included TPMT testing in its recommendations (Carter et al., 2004).
- There is not a formal evaluation of TPMT test and, the lack of consensus on TPMT testing across specialties makes the situation complicated. It is not clear whether not doing a TPMT test could incur in malpractice.
- Neither of the TPMT cost and economic studies studies have been considered in any of the decisions on TPMT testing.

9 Discussion

TPMT testing exemplifies a case where PM can improve the efficacy of licensed drugs. Even thoughTPMT was one of the first biomarkers of drug response discovered and the indications that testing could predict serious AEs, the test has not been added to the product license of AZA or 6-MP.

In 2003, the Department of Health (DoH) published a white paper announcing funding for research in PM and genetics and encouraging researchers to look for specialised service delivery mechanisms. According to this white paper, "...patients could undergo a test to predict their response or ensure medicine and doses are right at the first time". This was particularly relevant to patients at risk of AEs as, only in the UK, AEs were estimated to affect 7% of hospital admissions at an annual cost of £380 million to the NHS in England alone (DoH 2003).

In addition, the DoH added that "...the logistics and clinical utility of including a test in prescribing decisions will need careful evaluation, but applying this knowledge within primary care should significantly improve patient outcomes in medicines use" (DoH 2003). However, to date, TPMT testing has not received a careful evaluation by NICE or any other UK reimbursement body, even if TPMT is a well known biomarker and testing facilities are available at the NHS.

Since NICE launched its diagnostics assessment

programme in 2009, evaluations have focused on commercial diagnostics rather than home-brew tests (such as TPMT testing), even if these addressed an unmet need. This verifies the hypothesis that, the UK evaluation system for medical devices is not designed to address products for an unmet need, if these do not have business potential. But, despite the lack of institutional support, TPMT testing has been introduced in clinical practice through alternative routes. As we have seen in the drivers and barriers sections, the demand for testing increased considerably after two reference laboratories started offering testing (Ford et al., 2004a, Ford et al., 2004b, Birmingham City Hospital, 2009), followed by clinical associations including TPMT testing in their guidelines.

TPMT testing reference laboratories acted as lead users of the test, setting a national service across the whole NHS. These laboratories were also successful at optimising the technology for measuring the levels of enzyme in the blood and disseminating information about the benefits of testing.

The fact that two public laboratories have taken the lead in the UK and are offering TPMT testing services, indicates that:

- Expertise in product and service innovation in PM and diagnostic testing is not exclusive to the diagnostic or pharmaceutical industry. Other actors like public laboratories are important innovators, particularly in non-commercial diagnostics.
- The case of TPMT testing shows that, the implementation of PM for preventing AEs is strongly driven by lead users who reside in public hospitals. Clinicians and public laboratories are key actors designing the technological trajectories of PM for improving drug safety.
- PM for off-patent drugs is strongly associated to home-brew tests developed in NHS laboratories. However, private companies could threaten public service provision, if other commercial alternatives emerged and/or if alternative commercial tests were reimbursed.
- Peer opinion exerts a strong influence on clinical acceptance and demand for testing. Professional guidelines are strong drivers for technology adoption, for this reason, even though TPMT testing had not been appraised by NICE, it has been recommended by some clinical associations and requested by certain clinics and hospitals.

10 Conclusion

Market access for drugs and commercial diagnostics lies on the demonstration of safety, efficacy and cost-effectiveness, assessed by regulatory and reimbursement agencies. The case of TPMT testing, however, shows that PM for off-patent drugs is associated to non-commercial diagnostics. These do not follow the same evaluation procedures than commercial tests. The case of TPMT testing shows that, process of diffusion of these home-brew tests lies in public laboratories that generate testing capabilities and disseminate knowledge across the clinical community.

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