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25 years of knowledge creation processes in pharmaceutical contemporary trends

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Abstract. The pharmaceutical industry is knowledge and research-intensive. Due to technological, socio-political and organisational changes there has been a continuous evolution in the knowledge base utilized to achieve and maintain competitive advantages in this global industry. There is a gap in analysing the linkages and effects of those changes on knowledge creation processes associated with pharmaceutical R&D activities. Our paper looks to fill this gap. We built on an idiosyncratic research approach – the systematic literature review – and looked to unearth current trends affecting knowledge creation in international/global pharmaceutical R&D. We reviewed scientific papers published between 1980 and 2005. Key findings include promising trends in pharmaceutical innovation and human resource management, and their potential implications on current R&D practices within the pharmaceutical industry, from managerial and policy-making perspectives.

Key words: Knowledge creation, pharmaceutical industry, systematic review, global R&D.

1. Introduction

The pharmaceutical industry is research-intensive, and its competitiveness depends on continuous inventions and innovations. The ultimate embodiment of knowledge creation in the pharmaceutical industry is the successful commercialization of new drugs, and represents the key competitive factor

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Note: In this paper knowledge is used in its simplest Aristotelian definition as "justified true belief" (Nonaka & Takeuchi, 1995). Our focus on knowledge creation stems from the knowledge-based view of the firm, where knowledge becomes the primary resource/asset that confers a sustainable competitive advantage to the firm, promoting knowledge management to the most important organisational process within the firm (Blackler, 1995; Nonaka et al., 2001).

(e.g. Lipitor, the number one drug in 2005, sold 12,9 thousand million dollars, i.e. 2,3% of world-wide market sales) and the main means to recover high investments in R&D (in average more than 20% of total sales) and to cope with increasingly lower success rates (Atun, Gurol-Urganci, & Sheridan, 2007; Atun & Sheridan, 2007; Datamonitor, 2004; DiMasi, Grabowski & Vernon, 2004; IMS, 2006). It is a global industry, highly concentrated in terms of markets (about 90% of total sales in 2005 were in the Triad countries, i.e. US, Europe and Japan), and key players (top 10 firms had in 2005 more than 50% of worldwide sales), and is highly dependent on IP rights, specifically on patent protection (Arlington, Hughes, & Palo, 2002; Bierly & Chakrabarti, 1996; Class, 2002; Datamonitor, 2004; DiMasi *et al.*, 2004; Gassmann & Reepmeyer, 2005; Hayes & Walsham, 2003; Howells, 2002; IMS, 2006; Rousch, 2001; Salazar, Hackney, & Howells, 2002; Studt, 2003).

Recently, various factors have affected the operation and efficiency of pharmaceutical R&D processes, e.g. global markets, technology advances, the advent of biotechnology players, focus shifts on chronic diseases, stronger regulatory concerns regarding safety, price squeezes due to lower health budgets (particularly in Europe) (Attridge, 2007; Atun & Sheridan, 2007; Class, 2002; Gassmann & Reepmeyer, 2005; Thomas, 2004). The pharmaceutical companies have struggled to reduce the uncertainty associated to those factors, however few effects are visible, pace is slow, and little is seen in terms of efficiency increase in drug development.

A direct result of these new developments has been the rise of a *Research Industry* – new contract research organizations (CROs), some rivalling in size and influence the major pharmaceutical players, including most biotechnology firms. Arguably these new networks and the consequent research outsourcing have started to relegate the traditional pharmaceutical innovators to the role of global knowledge brokers and have put pressure on traditional knowledge creation processes in pharmaceutical R&D (Galambos & Sturchio, 1998; Gassmann & Reepmeyer, 2005; Hargadon, 1998; Martin, 2003; Mittra, 2007; Salman & Saives, 2005). The academic community has focused insufficiently on these matters, so the whole picture is rather "fuzzy".

Our research has struggled to reduce the fuzziness and analysed by means of a systematic literature review (Tranfield, Denyer, & Smart, 2003) a large number of scientific papers published between 1980 and 2005, which focused on international/global knowledge creation processes in pharmaceutical industry. We further present the methodology and results of this research according to the following structure. First, we discuss the systematic review methodology and share the protocol used to perform the review. Then we present and analyze data collected and we share the main results. Finally, we discuss the findings and point out relevant trends that may affect the knowledge creation processes in pharmaceutical context, including potential managerial and policy implications.

2. The Systematic Review Methodology: Brief Overview

The purpose of a systematic review is to provide a thorough appreciation of existing research in a specific field in order to promote evidence-based policy and practice. A systematic literature review starts with a research question/issue which guides the examination of the relevant literature (Macpherson & Holt, 2005a; Thorpe, Holt, Macpherson, & Pittaway, 2005; Tranfield *et al.*, 2003).

The history of the evidence-based systematic review was outlined by Tranfield *et al.* (2003), and incorporates lessons and methodologies considered relevant from the medical profession (e.g. Higgins & Green, Eds., 2005) to inform a protocol for systematic reviews in the business and management fields. The systematic literature review concept introduces a vigorous methodology that can be replicable, scientifically-minded and transparent. It aims to minimize bias via exhaustive literature searches of published material, while it provides an audit trail for the reader regarding the reviewers' decision processes, procedures and conclusions (Thorpe *et al.*, 2005; Tranfield *et al.*, 2003).

Our review drew from the general stages and protocols outlined by the study of Tranfield and colleagues (2003), complemented by insights provided by Creswell (2003). We considered three phases:

- Definition of the review scope and protocol;
- Data collection and analysis;
- Discussion of findings and implications on field reviewed.

3. Review Scope and Protocol

Scope

In defining the broader scope we went through an iterative process that determined the key parameters as follows.

The **primary objective of the systematic review** is to perform an exploratory study that increases the understanding of trends affecting knowledge creation processes in global pharmaceutical R&D.

The **issue addressed** is the impact of the new socio-political paradigm on the pharmaceutical industry, with a primary focus on knowledge creation processes. Since our outcome is connected to the **wider pharmaceutical context**, it will lead to new understandings and useful prescriptive suggestions regarding knowledge creation, management and policy making in pharmaceutical context and thus will inform future research in the global pharmaceutical R&D context or in other industries with similar characteristics.

Protocol

The protocol we have developed consists of a number of concrete conceptual steps. The first is to identify the relevant data for our review. Thus relevant papers for this systematic review would:

1. develop theoretical models of global pharmaceutical R&D and/or empirical papers that used qualitative, quantitative and mixed-methods. **Reasoning**: our review should not be biased either by method or by type (empirical/theoretical). Such a decision assumes that theory-based modelling as well as field work present credible views and understandings of the processes of knowledge creation in the industry.

2. cross-refer to organizations and institutions at different stages of development. **Reasoning**: we wished to avoid limiting ourselves to certain types of pharmaceutical companies, or companies that are under specific pressures.
3. focus on how knowledge and innovation networks for R&D are formed between pharmaceutical companies or/and with biotech companies and other partners. **Reasoning**: we wanted in particular to examine the results of environmental pressures (e.g. globalisation; new technologies; new political pressures) to the structures and organisational arrangements within the pharmaceutical industry. One of the major responses to these changes has been the formation of extensive collaboration networks and the formation of alliances with the biotech firms. This has led to knowledge creation, especially in the form of bio-science drugs.
4. be published in peer-reviewed journals. **Reasoning**: it is assumed here that peer-reviewed journals would ensure a higher quality and credibility of the source papers and thus would inform credibly the systematic literature review.

Thus in general our criteria for paper inclusion aim to separate material contextually (a focus on knowledge creation in the pharmaceutical industry) rather than methodologically or organisationally (by content).

Ineligible/irrelevant papers would:

1. analyse global R&D in other industries. **Reasoning**: our focus is the pharmaceutical industry
2. analyse aspects not related with global R&D. **Reasoning**: we aimed at companies that were affected dramatically by the major changes. For example globalisation would not affect a company with local R&D operations and local market orientation while the IT revolution would affect to a much lesser extent a company with a one country R&D orientation.
3. have been published before 1980; **Reasoning**: most of the major changes happened after the first biotechnology firms came to be. The IT revolution affected the industry even later, towards the end of the 1990s. Thus it made sense not to include publications before 1980. Furthermore a practical consideration has been that publications before 1980 are harder to locate online.
4. be written in other languages than English; **Reasoning**: we argue that the analysed knowledge domain is dominated by the English language. An additional practical consideration has been that both researchers shared advanced language fluency only in English.
5. include unpublished material, books, conference papers or other non-reviewed source of information. **Reasoning**: such data sources may not be as credible as peer-reviewed journals.

Primary data is extracted from scientific databases available to both reviewers, using specific search terms based on the above-mentioned inclusion and exclusion criteria developed conjointly. In order to test the asserted criteria we have devised a pilot search. In the pilot search we have also included Google Scholar, a freely available commercial search engine that specializes on academic material. In preparation for the pilot study, we built a classification system that would facilitate our review (Macpherson & Holt, 2005b). The search string for the pilot is developed in Boolean language to ensure comparability of results across databases. The choice of the terms in the search string is derived from the wider knowledge management and pharmaceutical R&D literature. The aim is to

segregate results on knowledge, pharmaceutical R&D, and globalization. The search string is presented here:

Pharmaceutical* AND (learn* OR innov*) AND (global* OR international*) AND (research OR R&D)

Once the pilot was completed, we revised the search string and the classification system. A detailed summary of the protocol thus developed is presented in Appendix 1.

4. Data Collection and Analysis

We started by performing the pilot study (see Appendix 2), as follows:

- Individual search in scientific databases, e.g. ProQuest (AB Inform), Elsevier (Science Direct), Sage, and Wiley Interscience aiming to determine how many relevant articles in total could be gathered. We examined top-10 results manually.
- Search on Google Scholar as to assess whether it would be comparable to the scientific databases. We analysed the top-20 results manually.

The pilot study revealed important issues.

First, that the same academic databases differed in each of authors' respective institutions, e.g. ABI Proquest encompassed 2,951 publications in one institution and 4,728 in the other. Most databases proved to have a different portfolio of access in each institution. Differential access made the conducting of a systematic and consistent literature review a particularly challenging task. Only Science Direct did not differ in literature scope; thus the search results for both researchers were identical. Other databases yielded consistent results but proved inadequate for our enterprise. Wiley Interscience did not yield any results, while Science Direct yielded a very small number of relevant articles and both were dropped.

The **second** issue was that each academic database has had different search facilities leading to a data gathering process that utilised different search parameters for each database. For example in ABI one could search text and citations combined while in Science Direct one could not. Concerning Google Scholar, it gave different results every time we ran the search string, a phenomenon that did not occur searching in the academic databases. That is attributed to the way Google creates and presents the results, where even our own search was affecting the order and number of results we were receiving!

The pilot study revealed two things: Google Scholar provided the most articles and in our pilot study it had the greatest number of relevant articles. We considered that it had great potential if used properly, as it brought together papers from a wide range of academic databases and it provided cached abstract when papers were not available. We concluded that Google Scholar was comparable, if not superior to academic databases.

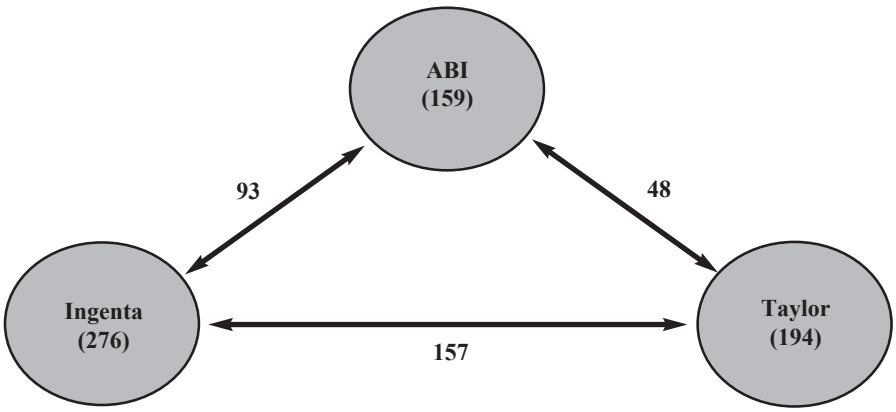
We added further qualifications and modifications to our search string:

Pharmaceutical innovation (knowledge OR learning OR learn) (global OR international) (research OR R&D) ISSN

The changes reflected partially the idiosyncratic nature of the Google Scholar search engine. The Google scholar tool automatically assumes an "AND" between words. The addition of the "ISSN" qualification assisted in focusing on published material. Furthermore, we restricted our search to "Business, Administration, Finance, and Economics" and "Social Sciences, Arts, and Humanities".

We used the refined search string in Google Scholar. Results were then input into Endnote. Our investigation looked at papers from the last 20 years and identified 672 papers potentially relevant to our search. These were then viewed manually. A total of 253 were removed (146 were institutional reports, working papers or other material that did not qualify as journal articles, 55 were books, and 52 were duplicate records). The remaining 419 articles were cross-examined for records in other databases. The results are portrayed in Figure 1.

Figure 1. Relationship of inclusion among records identified in Google Scholar Search with ABI (Ingenta and Taylor & Francis)



It was quite clear that Google scholar integrated results from all three academic databases. Ingenta and Taylor and Francis are explicitly and fully incorporated in the Google Scholar with links after every record leading directly to the appropriate entry in the database. Google contained more records than those that could be found in each academic database in isolation. However since ABI is not included in the Google scholar we could not conclusively say that Google contains all the possible records from ABI. The records from our population were identified manually. Only 40

records (about 10% of the total) were present in all three academic databases indicating that Google Scholar casts a much wider net of search than any of the other academic databases.

For an accurate classification of our data, we use two software tools: Endnote and NVivo. Endnote is more efficient in performing simple content analysis and assisted us originally with the categorization of the articles. The qualitative software NVivo is a useful tool for performing qualitative research (Hold, 2004; Richards, 2004) and is used here to analyse the abstracts of the most relevant articles, aiming to identify patterns. Thus we could identify potentially important trends and present their implications on current research and policy making, pointing out recommendations and insights on R&D practices and R&D management in pharmaceutical industry, a procedure consistent with similar systematic reviews in the management literature (Macpherson & Holt, 2005a; Thorpe *et al.*, 2005).

Once the sample was put in Endnote, we refined the classification system by adding two classification dimensions. The first separated articles into relevant, peripheral and irrelevant as determined by the presence or absence of our five core concepts. The second distinguished between theoretical and empirical material. This classification system further reduced the sample size of the articles and allowed for more detailed examination of our findings. However, a content search performed in Endnote revealed that it is rather difficult to identify articles that would be primary according to our original classification scheme, which was based only on abstract and title content analysis.

It became quickly apparent that the original Google search examined the whole article rather than just the title/abstract combination. This led to a relaxation of our original requirement for primary (presence of all five core concepts in the article). Four concepts would suffice to label an article as primary while 3 terms would label it peripheral. Based on this reviewed classification scheme, we categorized the 419 papers in Endnote, based on individual abstract analysis performed by the two reviewers conjointly (to ensure validity). We obtained 45 relevant records for our qualitative analysis. These articles (see Appendix 3) were isolated in another Endnote library and their titles and abstracts were exported to an NVivo project. A roadmap of the review scope and protocol can be seen in Figure 2.

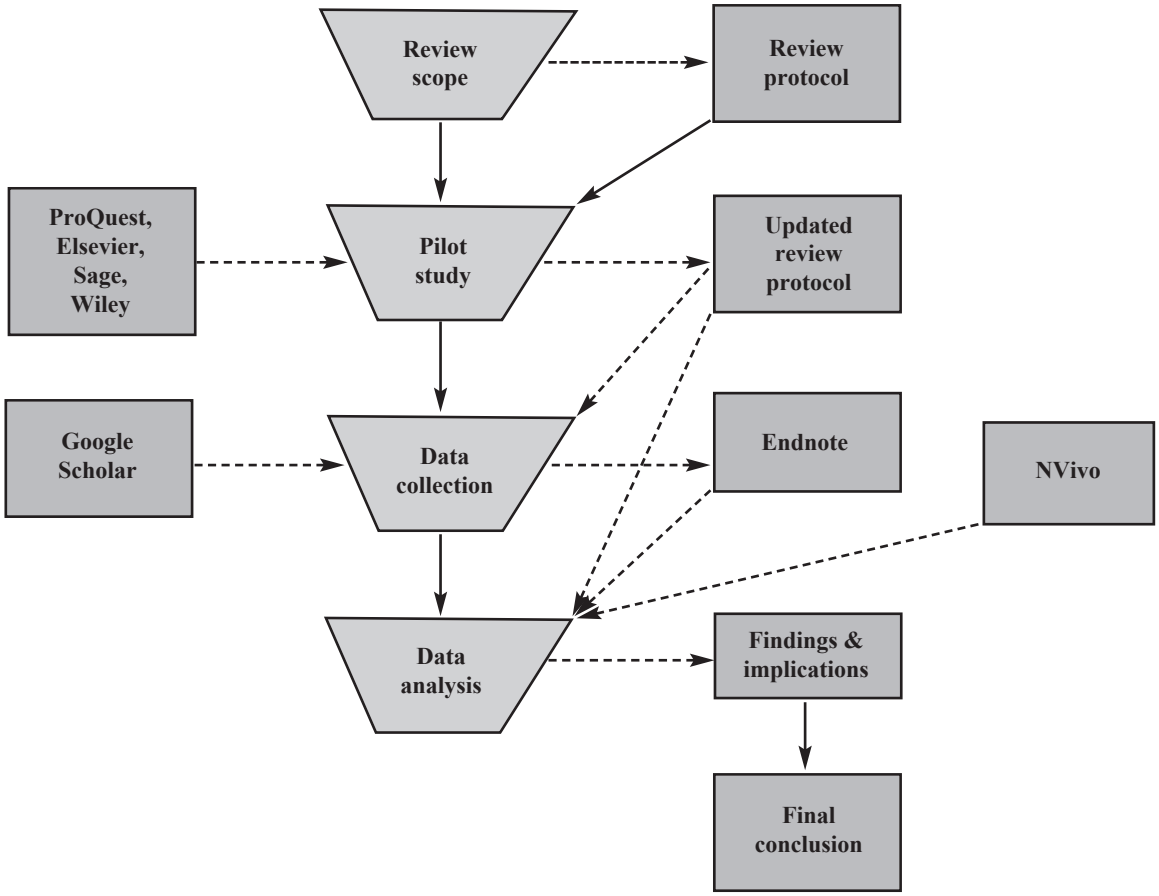
The NVivo approach was two-pronged.

First a grounded-theory approach was used to identify the key concepts. One reviewer performed free coding on all 45 abstracts and built a hierarchical tree of respective codes. Similar codes were merged and a final model was built in order to most objectively describe the nature and quality of the information contained in the abstracts examined. Via an iterative process the final hierarchical model was synthesized. This model is presented in Appendix 4, whilst statistical data on which themes appeared more frequently in the analyzed records are illustrated in Appendix 5.

As it can be observed from the model, the considered abstracts indicate extensive links between the pharmaceutical industry and, mainly, biotechnology, with a few links to the paper, food and forestry (!) industry (can be considered an outlier). 58% of all records pointed to linkages to other industries (predominantly Biotechnology). This is an indication of the pharmaceutical industry's efforts to complement existing knowledge by creating synergies with this emerging industry. This result is hardly surprising.

34% of all records considered the pharmaceutical industry's context. Issues like the new scope of health, the role of customers are mentioned and the emphasis given to regulatory issues (85% of

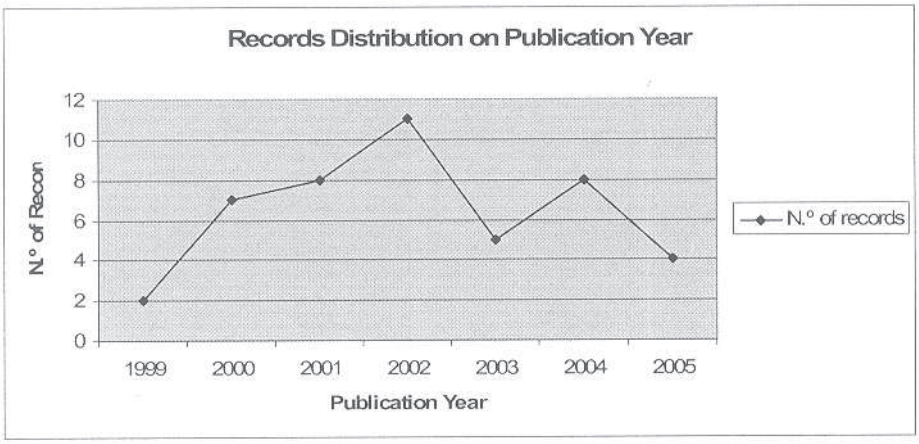
Figure 2. Roadmap of the Systematic Literature Review



all records relating to context) reflects an important concern of its relevance/impact to the business and its innovation patterns. We also note a specific interest given to patenting (free circulation of knowledge and uniform rules versus tighter enforcement of patents). This also came as no surprise, since we analyzed knowledge processes in a knowledge-intensive and global industry, where regulations and patenting play an important role in securing knowledge creation and determining knowledge distribution and exploitation.

Under the globalization heading, issues like distributed production, distributed innovation, new organizational forms and increasing competitiveness (e.g. networks, strategic alliances, mergers, clustering) as well as technological interdependence are at the core of analyzed material. However, more interest was shown to distributed innovation and the subsequent exploitation of innovation resources all over the world to enhance the efficiency of the drug development process. New organizational forms were also at the core of academic discourse, with particular emphasis given to the importance of localization (89% of all records in the Globalization category). This is also to be expected in a global context.

Figure 3. Records' Distribution on Publication Year (all 45 considered for qualitative analysis)



In addition, pharmaceutical industry appeared to look into rigorous HR management practices, giving emphasis to knowledge workers' autonomy, to knowledge sharing between them and to the creation of a global mindset among these workers (e.g. mobility, knowledge combination). 24% of the records gave importance to HR management and the role of knowledge workers, covering issues linked to their desirable autonomy to exploit duly their competences.

Second, and in order to validate the original coding, the other reviewer utilised the developed framework and applied it to re-code the abstracts and titles of the 45 articles. The re-coding was done independently (the second coder had no knowledge of results of the first coding). The desired outcome was to test the robustness and external validity of the framework previously developed. It also gave space to revise the internal validity and reach an agreement over both construct and concept validity of the hierarchical tree.

Results proved quite positive. The hierarchical tree was revised yet not substantially. There was some reshuffling and some new codes developed (see Appendix 6). There was an estimated 15% difference between the node structure of the hierarchical tree of the first reviewer and the second. This indicated that the result was a robust construct with a relatively high degree of internal validity.

There were differences in the percentages coded under each node (see Appendices 5 and 7). Mostly the second coding pushed up the percentages of three of the four main nodes (context/industries/ globalisation) by 20-5%, which indicated that second coding considered broader understandings of the concepts than the first one. That may be a direct result of the fact that the second tree had fewer nodes due to additional reiterations by the authors. The only notable exception was in the fourth, the HRM parent node where the second author actually seemed to have taken a more limited understanding of the node than the first author.

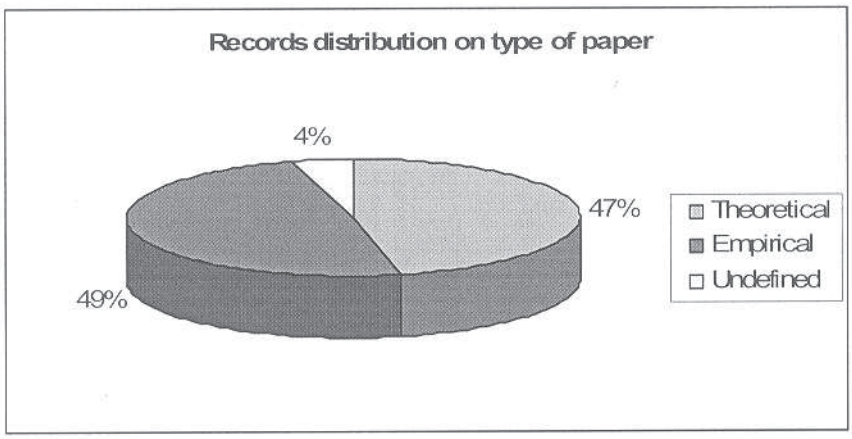
Another interesting issue was that in this second phase, context became more important (63% of all records). Same happened to knowledge production, research intensive networks, importance of funding, localization in clusters, networks and internationalization of technology. However, the main conclusions

remained intact, which reinforces the validity of the model and its capacity to describe accurately the analyzed records.

Alongside the coding, statistical data was gathered as to the publication year of each paper and their empirical or theoretical base wherever it was possible to identify. Interestingly, papers' distribution by publication year (as Figure 2 portrays) reflects how the field of knowledge creation in the pharmaceutical R&D context has only recently been addressed by the academic community.

The filtered records of our analysis were published between 1999 and 2005. We recall that our search covered papers with publication date from 1980. This may signify one of two things: either issues related to globalization of innovation and knowledge production processes in the pharmaceutical industry fell into academic attention only after 1996-7, or that databases used by Google Scholar only made available papers published in the last 7-8 years. The first explanation is more plausible since Ingenta and other databases, which are already included in the Google Scholar, contain data much before 1996.

Figure 4. Records' Distribution on type of paper (all 45 considered for qualitative analysis)



As of the empirical – theoretical distribution, the classification work was performed conjointly by the two researchers. 49% of the papers were theoretical and 47% were of empirical nature, which indicates an equilibrated distribution. If we go back to the roots of systematic reviews, we note that usually only empirical works were considered for this kind of studies. Yet, theoretical papers can provide particularly good insights and should be, in our opinion, considered for the purpose of a systematic review.

5. Findings

Summarizing, key identified trends that affected knowledge creation processes in pharmaceutical industry during the analyzed period were the following:

- Strong linkages with the biotechnology industry;
- High influence of and importance given to regulatory environment, with contradictory tendencies on knowledge freedom and protection;
- Strong emphasis on the globalization issue, with focus on distributed innovation (especially linked with knowledge production), new organizational forms to better deal with it (emphasis given to funding, clusters and networks) and technology (especially internationalization of technology);
- Emerging issues like the new scope of health and competences (knowledge workers' autonomy and global mindset).

Looking at these trends, a first insight is that new knowledge creation in pharmaceuticals and its linkage to aspects of localization, regional funding, global regulations needs yet to be properly addressed; further study is required to identify appropriate (and more flexible) methods and instruments to perform the knowledge creation processes efficiently. A conspicuous absence in our findings is that of the information technology (IT) as a factor. Very few articles refer to its importance in knowledge management, even though it is frequently mentioned in generic knowledge management literature (e.g. Cabrera & Cabrera, 2002; Gray, 2001; Lerer & Piper, 2003; Nonaka, Reinmoller, & Toyama, 2001). This could indicate either that pharmaceutical industry has not made much progress on IT-based KM or that the search should have focused on IT usage in fields related to the pharmaceutical industry such as bioinformatics or that the advances in IT are secretive and there is little public information. In addition one should note that certain technologies such as genomics, proteomics and even the field of biotechnology are implicitly yet certainly based on IT (Galambos & Sturchio, 1998; Howells, 2002; McMeekin & Harvey, 2002).

Localization issues focus on clustering and networks. It is unclear from our data whether this is evidence of the emergence of a network society or the natural evolution of simpler approaches based on regional/local agglomeration of specialized knowledge i.e. universities or specific research organizations. Future research should consider whether clustering is an appropriate way to look at localization issues, whereas other simpler explanations could be considered. The bewildering variety of cluster/network arrangements found in the review may indicate that scholars either are unclear of the investigated phenomena, or that their rhetoric in pharmaceutical R&D literature has advanced way beyond the actual developments in the industry. However, armed with the information obtained on publication dates one would probably side with the former version, i.e. lack of clarity. Pharmaceutical industry is a relatively slow industry and the ideas of clustering, networks and national innovation systems were developed in the early 1990's. Thus the relative dearth of articles before 1996 may indicate that pharmaceutical firms or the academics have not caught up with changes brought about by

these new organisational arrangements (networking and clusters), new IT and technology developments (biotechnology, genomics, proteomics), and changes in regulation regime.

In what concerns the role of knowledge creation in global pharmaceutical R&D it is addressed only indirectly in the analyzed records, in terms of innovation and general regulations. Knowledge creation seems to underlie all strategic decisions of global pharmaceutical R&D but as a process is never put explicitly in focus. However the role of knowledge processes is discussed, especially when it comes to distributed innovation and HR management. Thus more studies that focus explicitly on the role of knowledge creation in pharmaceuticals or on the systematic management of knowledge processes may help revealing efficient management practices both for research and general strategy in the pharmaceutical industry.

6. Policy implications

The identified trends may serve as inspiration to policy-makers, as follows.

Institutional mechanisms and incentives may be further developed at international levels in order to enhance cooperation with the biotechnology partners and to complement the current tendency of limited collaboration initiatives with commercial ends. This is important so as to stimulate cooperation between pharmaceutical firms and biotechnology ones, especially in the discovery phase, and thus to facilitate a common language between these partners. It may increase competitiveness on both sides and benefit patients, while increasing the available knowledge base for timely embodiment in new products and services.

Policy makers should include a global mindset, a global reasoning in their approaches. If pharmaceutical industry and the knowledge creation processes for new drug development are global, albeit concentrated in Triad countries (only lately more open to other developing countries, too), what reason is it to make nationally bounded policies for such an industry? We believe policy makers could be true knowledge workers with global perspectives and collaborate with the pharmaceutical industry, biotech partners, regulatory authorities, decision makers (physicians, pharmaceutical profession, patients) so as to benefit all actors of an increasingly global society.

Regulatory entities should continue working at an international level to achieve consensus and harmonize regulations, in order to relieve pharmaceutical firms from increasing and unnecessary paper work and time losses. ICH (International Conference for Harmonization) in its effort to define good practices for R&D and production is one step in the right direction; it needs though to be further developed. EMEA's work on European pharmaceutical market is another good step, by approving medicines for usage in any European market; however pricing is still established nationally and process is difficult and longer than it should be. A desirable development would be setting up market entry process valid for several key countries, with pricing and remaining details processed batch-like with common requirements. By reducing time-to-market and harmonizing regulations there is more time and money for knowledge creation and commercialization.

And maybe if all the funds spent on bureaucracy would be spent on ethical, less profitable research on cures for orphan diseases (e.g. malaria, or other developing countries' devastating plagues) there may be a way to address the paradox between freedom of knowledge and the corresponding need for protecting it.

7. Conclusions

Pharmaceutical innovation is paramount now more than ever as the environment constraints increase and the market becomes more competitive. New knowledge creation is the key way to expand the markets ahead of the increasing global constraints and various market pressures. So while the pharmaceutical industry expands its networks and enhances its HR practices, it has to pay attention to how the new arrangements enhance its knowledge creation processes or dilute the existing capacities to create new knowledge. The global element becomes more and more prominent and the companies have to consider it in their calculations for further expansion and growth.

Knowledge work implies a certain degree of freedom. Human resources from this industry are increasingly considered knowledge workers, and are given considerable autonomy to create and utilize knowledge in order to respond to existing challenges and prepare for new ones. Pharmaceutical R&D managers are viewed as knowledge managers and their behaviour and management practices have to adjust accordingly so as to inspire their subordinates and colleagues to think globally and creatively. This empowerment and flexibility is reflected in the rise of the new organisational forms and networks prominent in the results of this study. Thus, as the R&D function mutates and changes to meet this new and daring knowledge world, possible structural arrangements diversify accordingly to meet the challenge. Yet the pharmaceutical industry has witnessed increasing regulation and the organisational knowledge processes seem intimately related to knowledge protection patterns and institutional regulations. The heavy regulatory environment would be expected as health is a sensitive issue. There are concerns about biotechnology, about the harmonisation of regulations for the benefit of the public, there is talk about the new scope of health and pressure to reduce prices and increase safety. However it highlights a potential friction between the freedom implied in new knowledge production and the pressure for regulation, a dialectic that is transparent and prominent in our research. This may have detrimental effect to the capacity of the industry to innovate in the long term, and a new balance between regulation and creativity should be seriously considered by policy makers, especially in the Triad countries.

With a two century experience in research and a historical resilience to various socio-economic and technological upheavals, the pharmaceutical industry has repeatedly proven its flexibility and adaptability to new challenges. Probably the key conclusion of this research, tentative though it may be, is that we lay in the middle of dramatic changes regarding the way knowledge creation is pursued by contemporary pharmaceutical R&D processes, yet their effects in the pharmaceutical knowledge base are still fuzzy. It may take several years before we have a clearer picture of what structures of global pharmaceutical R&D will prevail in the industry's constant efforts for knowledge

creation and innovation. Thus a need to ascertain the new paradigm will require another thorough systematic review that may clarify the fuzzy elements that we identified.

We end with a short note on the methods used in this article. The rigorous classification and analysis of the results from the Google scholar database search has provided us with an initial sample of almost 700 papers pertaining to pharmaceutical innovation and knowledge creation in a global setting. We then considered a bit more than 400 papers for our initial classification and around 10% of that were retained for qualitative analysis. Even by using strict criteria to perform searches, technical limitations of the database search platform may require a human double-check of results. In the case of Google Scholar, as it only performs search on full text and does not allow search refinements to abstract and title, the number of final relevant records was quickly diminished. This then casts some doubt to the original assessment that the Google Scholar may be superior to the academic databases. Even though it evidently provides far more hits per category and is much broader in scope than academic databases, its limited search engine does not allow sophisticated searching and thus renders the breadth advantage meaningless.

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Resumo. A indústria farmacêutica baseia-se na utilização intensiva de conhecimento e na investigação e desenvolvimento de novos medicamentos. Devido às mudanças tecnológicas, sociopolíticas e organizacionais, a base de conhecimento utilizada para conquistar e manter as vantagens competitivas tem estado a evoluir constantemente. Existe uma lacuna na análise das relações e dos efeitos daquelas mudanças nos processos de criação de conhecimento associados às actividades farmacêuticas de I&D. O nosso artigo procura colmatar esta mesma lacuna. Recorremos a uma abordagem original de investigação – a revisão sistemática da literatura – e procurámos identificar as tendências que afectam actualmente a criação de conhecimento nas actividades de I&D internacional/global. Considerámos na revisão artigos científicos publicados entre 1980 e 2005. Os principais resultados incluem as tendências promissoras na inovação farmacêutica e na gestão de recursos humanos, e as suas potenciais implicações nas práticas actuais de I&D na indústria farmacêutica, considerando as perspectivas da gestão e da governação.
Palavras-chave: Criação de conhecimento, indústria farmacêutica, revisão sistemática da literatura, I&D global.

APPENDIX 1

— Summary of the protocol —

Steps	Criteria	Checks
Study identification (inclusion or exclusion)	Global R&D in pharmaceutical and knowledge processes, focus on knowledge creation.	Cross-read the paper/abstract to ensure that the search equation is respected. This is important as database search may fail.
Assessment of quality	Scientific publications, and reviewers' conjoint evaluation (in case of doubt, with justification and record of the rationale).	ISSN, citation statistics (if available), number of links in Google (if available).
Data collection and extraction	Trends affecting knowledge creation in global pharmaceutical industry. Usage of Endnote software for storage and subsequent analysis.	Ensure the comprehension of the knowledge creation concept is the same as reviewers' understanding.
Data analysis	NVivo software/grounded theory approach to codification.	Double coding to ensure validity.

APPENDIX 2

— Results of the pilot study —

GENERIC RESULTS

				Number of results				
Search string	**Scope**	**Date of search**	**Date range**	**Sage**	**Wiley**	**ABI**	**Science Direct**	**Google**
Pharmaceutical* AND (learn* OR know*) AND innov*	Title and abstract	10 Jan 2005	1980-2005	312	0	128	53	208
AND (global* OR international)	Title and abstract	10 Jan 2005	1980-2005	273	0	39	52	183
AND (research OR R&D)	Title and	10 Jan 2005	1980-2005	270	0	25	50	182

SAGE (EXAUSTIVE SEARCH)

Selected results	Primary	Secondary	Peripheral	Conceptual	Irrelevant	Comments
10	0	1	2	0	6	1 record difficult to evaluate.

ABI (EXHAUSTIVE SEARCH)

Selected results	Primary	Secondary	Peripheral	Conceptual	Irrelevant	Comments
10	6	3	1	0	0	Good results, apparently relevant. However, small initial sample (25 results only).

SCIENCE DIRECT (EXAUSTIVE SEARCH)

Selected results	Primary	Secondary	Peripheral	Conceptual	Irrelevant	Comments
10	2	0	0	0	8	Mainly irrelevant results.

GOOGLE (EXHAUSTIVE SEARCH)

Selected results	Primary	Secondary	Peripheral	Conceptual	Irrelevant	Comments
21	1	0	6	0	10	A single relevant record. Six peripherals. High initial sample (182).

APPENDIX 3

— Records considered relevant for qualitative analysis —

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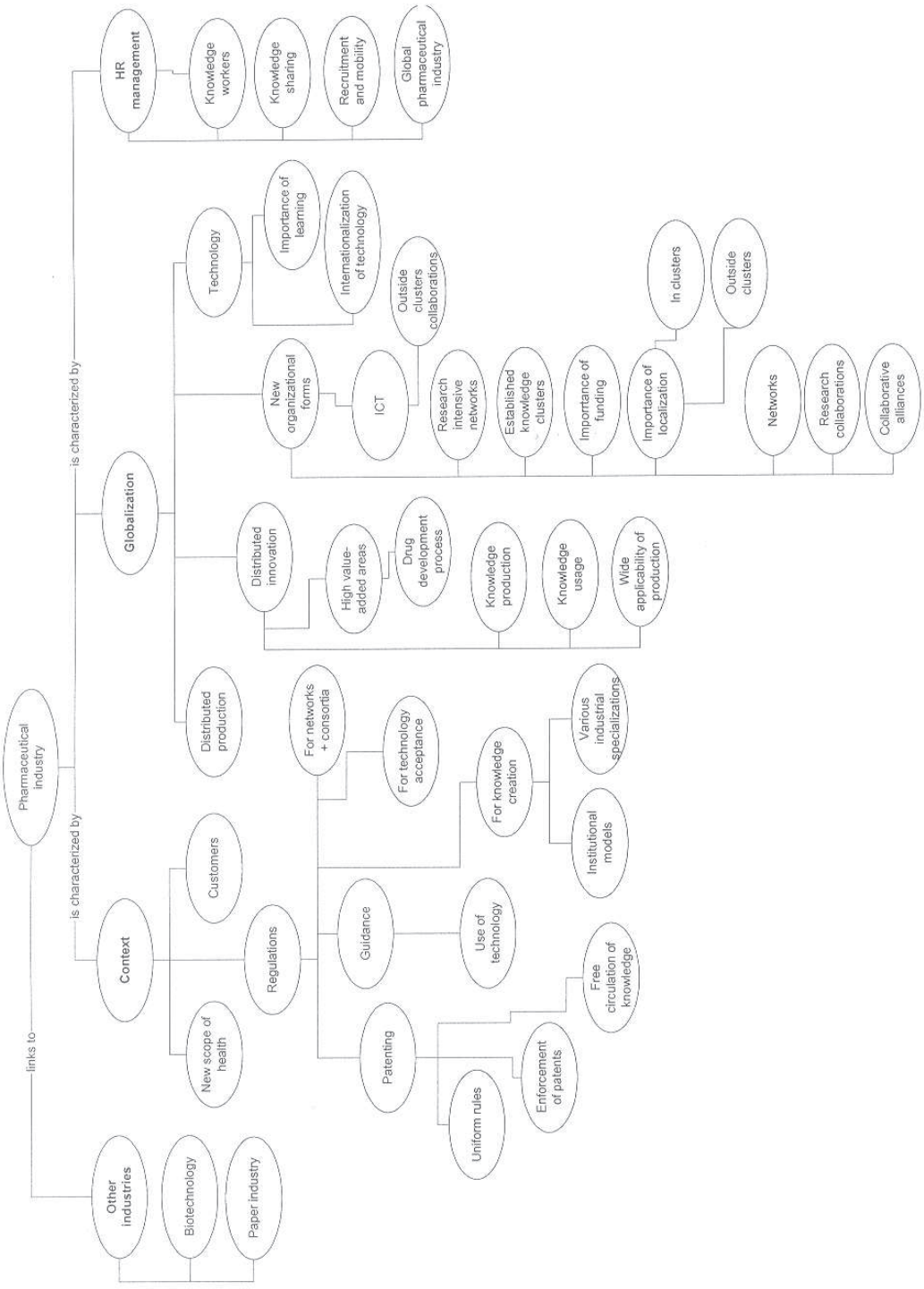
APPENDIX 4

— NVivo model after grounded theory approach —



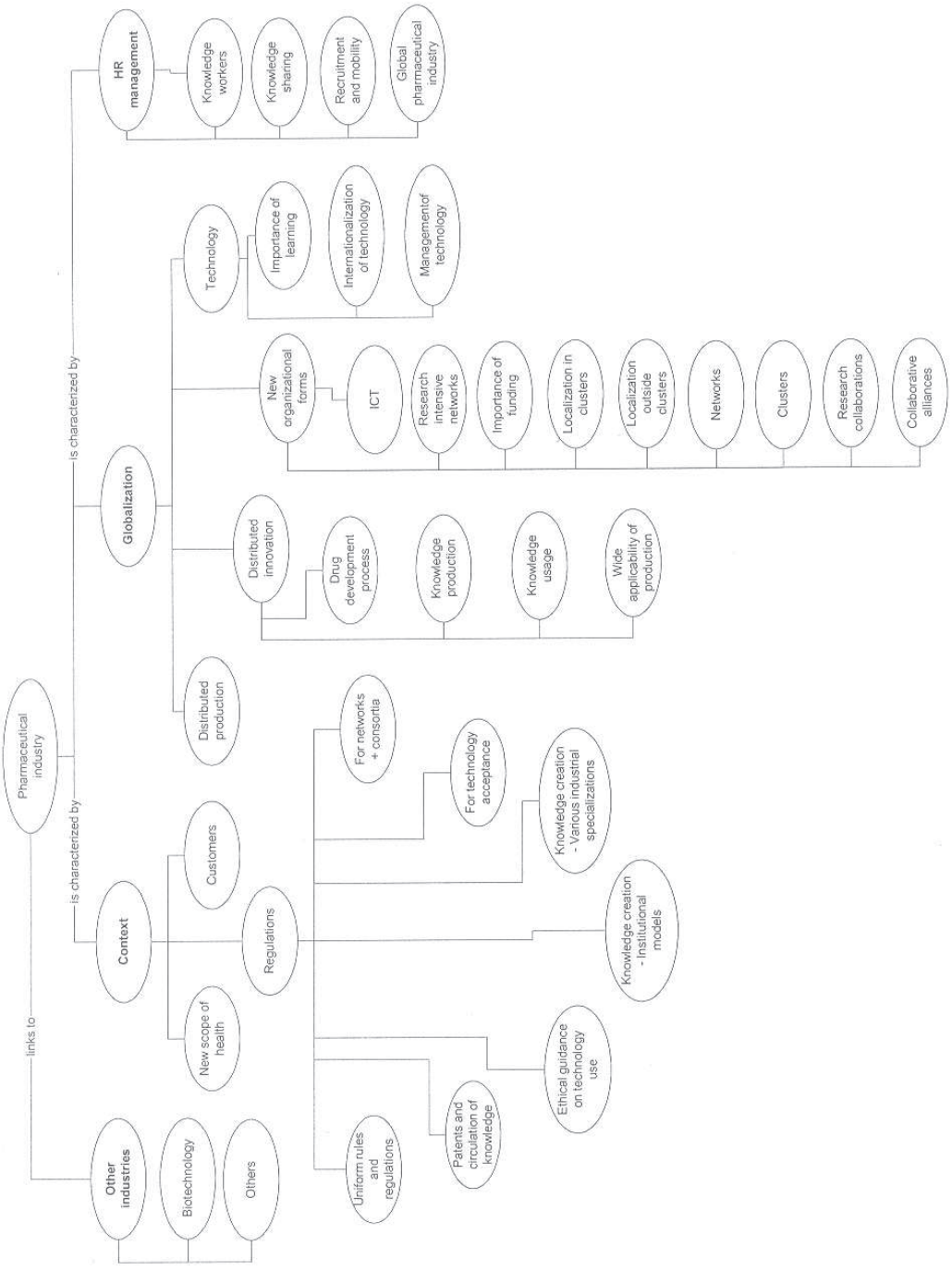
APPENDIX 5

— Statistical data on NVivo model (grounded theory approach) —

Theme	Number of records	% of parent	% of all
Pharmaceutical industry	38	**100%**	**100%**
Other industries	32	**58%**	**58%**
Biotechnology	29	**86%**	**50%**
Paper industry	1	5%	3%
Context	13	34%	**34%**
New scope of health	1	8%	3%
Customers	1	8%	3%
Regulations	11	**85%**	**29%**
Patenting	5	**45%**	**13%**
Uniform rules	3	**60%**	8%
Enforcement of patents	1	20%	3%
Free circulation of knowledge	1	20%	3%
Guidance	2	18%	5%
Use of technology	2	**100%**	5%
For knowledge creation	1	9%	3%
Institutional models	1	**100%**	3%
Various industrial specializations	1	**100%**	3%
For technology acceptance	1	9%	3%
For networks and consortia	2	18%	5%
Globalization	19	**50%**	**50%**
Distributed production	2	11%	5%
Distributed innovation	11	**58%**	**29%**
High value-added areas	5	**45%**	**13%**
Drug development process	4	**80%**	**11%**
Knowledge production	3	27%	8%
Knowledge usage	2	18%	5%
Wide applicability of production	1	9%	3%
New organizational forms	9	**47%**	**24%**
ICT	3	33%	8%
Outside clusters collaborations	1	33%	3%
Research intensive networks	1	11%	3%
Established knowledge clusters	1	11%	3%
Importance of localization	8	**89%**	**21%**
In clusters	6	**75%**	**16%**
Outside clusters	2	25%	5%
Networks	2	22%	5%
Research collaborations	1	11%	3%
Collaborative alliances	1	11%	3%
Technology	3	16%	8%
Importance of learning	1	33%	3%
Internationalization of technology	1	33%	3%
HR management	9	24%	**24%**
Knowledge workers	4	**44%**	**11%**
Knowledge sharing	1	11%	3%
Recruitment and mobility	2	22%	5%
Global pharmaceutical industry	1	11%	3%

APPENDIX 6

— NVivo model after second (independent) review —



APPENDIX 7

— Statistical data on NVivo model (after second review) —

Theme	Number of records	% of parent	% of all
Pharmaceutical industry	38	**100%**	**100%**
Other industries	26	**68%**	**68%**
Biotechnology	24	**92%**	**63%**
Others	5	19%	**13%**
Context	24	**63%**	**63%**
New scope of health	3	13%	8%
Customers	1	4%	3%
Regulations – Institutions	23	**96%**	**61%**
Uniform rules and regulations	3	13%	8%
Patents and circulation of knowledge	3	13%	8%
Ethical guidance on technological use	9	38%	**24%**
Knowledge creation – Institutional models	2	8%	5%
Knowledge creation – Various industrial specializations	4	17%	**11%**
For technology acceptance	2	8%	5%
For networks and consortia	7	30%	**18%**
Markets	4	17%	**11%**
Globalization	29	**76%**	**76%**
Distributed production	3	10%	8%
Distributed innovation	16	**55%**	**42%**
Drug development process	4	25%	**11%**
Knowledge production	10	**63%**	**26%**
Knowledge usage	2	13%	5%
Wide applicability of production	1	6%	3%
New organizational forms	18	**62%**	**47%**
ICT	1	6%	3%
Research intensive networks	4	22%	**11%**
Importance of funding	5	28%	**13%**
Localization in clusters	7	39%	**18%**
Localization outside clusters	2	11%	5%
Networks	6	33%	**16%**
Clusters	6	33%	**16%**
Research collaborations	1	6%	3%
Collaborative alliances	2	11%	5%
Technology	9	31%	**24%**
Importance of learning	2	22%	5%
Internationalization of technology	1	11%	3%
Internationalization of technology	5	**56%**	**13%**
HR management	7	18%	**18%**
Knowledge workers	4	**57%**	**11%**
Knowledge sharing	2	29%	5%
Recruitment and mobility	2	29%	5%
Global pharmaceutical industry	3	**43%**	8%