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Risk Assessment of Innovations in the Biopharmaceutical Industry

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1. Introduction

First, the chapter summarizes the specialties, which are appeared in the red (medical) biotechnology in the occurrent risks/uncertainties point of view. Then it draws attention to the fact that part of the literature about risks/uncertainties (for example in the environmental literature) serve as a broad basis for the analysis and evaluation of uncertainty. This seems also useful for the examinations of the uncertainties in the medical biotechnology, but as far as we know, it is not applied. Finally, the third part of the chapter follows a new analysis and it introduces that there is an uncertainty dilemma in the research of the medical biotechnology, which can be reduced, but can not be eliminated.

2. Biotechnological innovations and trends

Biotechnology is spreading rapidly in the pharmaceutical, environmental protection, agricultural, and other industrial environments. The number of molecules produced by biotechnological methods is growing rapidly, thanks to new methods and an almost exponentially increasing knowledge base.

The appearance of novelties is very fast. There is a significant technological leap, from time to time. These radical innovations are aimed at solving complex problems by implementing and integrating new technologies. Radical innovations that lead to disruptive technological development in biotechnology based industry and especially in red biotechnology are usually result of long term research. These innovations provide a broad platform for a new regime in technology, from time to time [1]. At the same time, disruptive innovation is not necessarily radical. Small innovations can also have great disruptive economical influence, provided they are introduced in a new milieu. Just think about the turning to containers in oversee ship cargos, for example, when containers had already been much earlier utilised in other areas of transport.

Companies were forced to cooperate due to the high risk associated with biotechnology, the complexity of strategic management rules and the unusually high amount of needed funds. First of all, the necessary monetary tools are available only at the largest companies. Second,

the necessary competencies are often missing with smaller companies. For example, a smaller company, a market leader in R&D, most probably does not have the necessary experience either of the capability needed to clinical testing or production. Cooperation is necessary to fill these gaps. With this sharing of different sorts of risks will be realised. These risks - actually non-calculable uncertainties several times, or at least the calculations can not be serve as reliable planning tools - may be technology, market, regulatory or competition related. The competition related one reflects on the segments of all the other risks, since the rapid development of China, South Korea and India. The only comparative advantages can only be quality and knowledge the traditional pharma producing countries have. But precisely these are areas where China and India are developing rapidly, while maintaining the seemingly natural price advantage. Europe and the USA can only compete with these products if they do not count on price advantage, but on therapeutic advantage. This means producing a newer, better molecule, first of all. However this larger added intellectual value brings larger risks, uncertainties on behalf of technological, market and registration. These tendencies are also catalysts of cooperation, for cooperation means some risk sharing.

It is precisely these different, but interrelated risks that make pharmaceutical biotechnology complex. To successfully manage complex processes and instability necessitates cooperation. Instabilities are cross-linked. They can even strengthen or weaken each other. An example of mutual strengthening of uncertainty is the technological uncertainty of producing a new molecule, and the registration and legalization which follow. Registration gives the same molecule an added economical value and can, if it is registered already, decrease market instability, since it can become a market leader, a so called "blockbuster"[1], with multi-million dollar yearly turnover.

Drug manufacture is a multinational phenomenon, with an active global trade in intermediates (specialty chemicals), active pharmaceutical ingredients, and finished products. R&D, by contrast, is much more geographically concentrated; the bulk of all R&D expenditure occurs in the United States, a handful of European countries, and Japan. The pharmaceutical value chain encompasses many activities, ranging from basic scientific research to marketing and distribution. Innovation in the industry is tightly linked to basic biomedical science, and many companies participate actively in basic scientific research that generates new fundamental knowledge, data, and methods.

Drug discovery includes basic science and research on disease physiology, identification and validation of "druggable targets" in the body where therapeutic molecules may affect disease processes, identification and optimization of drug candidates, and preclinical testing. The development phase of research focuses on testing in humans, from the first small-scale trials directed at establishing basic physiological data in healthy volunteers through to large-scale trials on patients having the disease, which are designed to provide data on safety and efficacy to support applications for regulatory approval of the drug. Following marketing approval, research often continues to develop improved formulations of the product and to establish safety and efficacy in treatment of additional diseases or patient populations. Reflecting extraordinary advances in biology and biochemistry since the 1970s, the industry has become progressively more science intensive, relying closely on

[1] A blockbuster drug is a drug generating more than $1 billion of revenue for its owner each year.

fundamental advances in physiology, biochemistry, and molecular biology rather than "brute force" application of large-scale resources. If anything, this process has accelerated over the past decade as the industry has focused on complex and systemic diseases such as cancer, autoimmune diseases, and psychiatric conditions. Particularly in drug discovery, industrial and publicly funded research efforts are deeply intertwined.

Rapid growth in technological capabilities in low-cost emerging economies is presenting new opportunities and challenges for pharmaceutical companies. Some geographic redistribution of R&D activity does appear to be taking place. On the one hand, companies located in countries such as India and China are performing more in-house R&D oriented toward developing new drugs, rather than reverse-engineering existing products or improving production efficiency. On the other hand, reflecting the general trend of the industry toward greater specialization and external sourcing of R&D services, OECD-based companies are beginning to look to low-cost countries as suppliers of contract research services, and growing numbers of clinical trials are being conducted in emerging economies. India and China are the two countries most frequently mentioned in this regard; however, by some indicators significant growth in activity also appears to be taking place in some Eastern European countries, Argentina, Brazil, Taiwan, South Africa, and Israel. Over the past decade, the biotechnology industry has been the focus of increasing academic and policy interest as a potential source of regional and national economic development [2] [3].

Historical development of biotechnology can be divided into several large eras [4]:

- The period started with the first conscientious use of biotechnology. This process started in the second half of the XIX century (about 1865), when Pasteur discovered that fermentation is caused by microorganisms. After understanding the essence of this process through microbiology, its industrial application became feasible. The beer and alcohol industries developed, vinegar and lactic acid production began. The production of ethanol, butanol, acetone, glycerin, citric acid etc. through fermentation began.
- The discovery of antibiotics provided the momentum for the second great leap around 1940. The productivity of microorganisms was increased by biological, genetic and biochemical methods (mutation, selection). Building on these opportunities and the rapid development of fermentation techniques, the result was a veritable technological revolution. The most important results were the large scale production technologies of antibiotics, amino acids and enzymes.
- The next phase started in the first half of the 1970-s. The essence of this new biotechnology is that by altering the heritable material of living beings, through a conscious and planned manner, results in the development of new characteristics. Through the use of recombinant DNA and cell fusion, humans begun to alter the characteristics and functions of living organisms to suit their needs.
- The fourth era is linked to the first commercial sale of human insulin (1982). This is the first member of the rDNA pharmaceutical products, meaning the large scale distribution of the products of the previous era. Thus growth gained even more momentum.
- The fifth era can be marked by the latest great innovation, on one hand, the cloning of animals by the use of a cell nucleus, the creation of "Dolly" (1997) and later other cloned animals and on the other, the completion of the "Human Genome Project" (2000).

To make expectations essentially belongs to the development of new technologies. Many people see biotechnology as the industry of decisive strategic importance, following informatics at the start of the XXI century. According to optimistic forecasts, by the middle of the next decade, the pharmaceutical and biotechnology industries will become the leading industrial branches in the world, surpassing information technology and telecommunication. (In this article we will only concentrate on red (medical) biotechnology.) Expectations regularly realise some cyclic dynamic. One can argue that elements in that dynamic follow each other by necessity. Following the first hope even deep disillusion can be the next step as it was with the ecommerce bubble around the turn of the century. While with biotechnology the hope phase is still very strong, with time delay, unexpectedly raising costs, etc. in comparison to optimisticforecasts, the hope phase can partially turn into disillusion urging to change the earlier expected enthusiasm into more "rational" thinking.

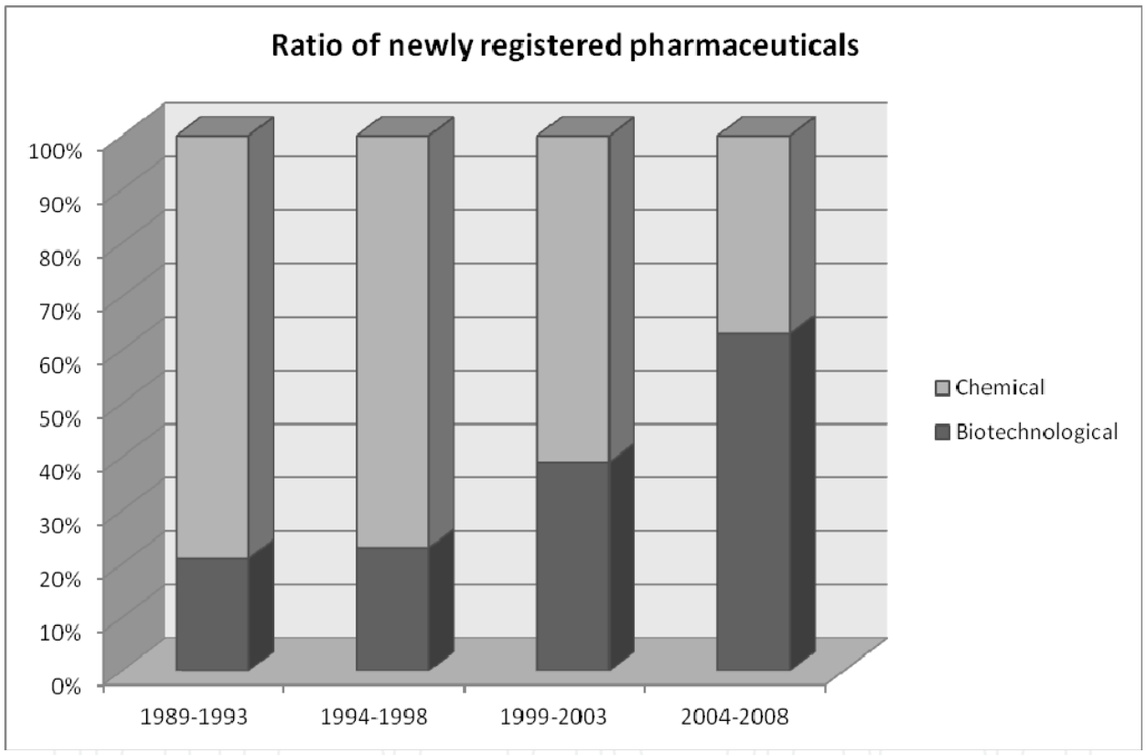

Fig. 1. [1] based on [7]: Ratio of newly registered pharmaceuticals: chemical and biotech entities.

The EU considers the development of the biotech industry in view of the pharmaceutical industry exceptionally important and is rather optimistic about its future and the role the EU can play in it. This means strengthening collaboration between the two sectors [5]. Biotechnology plays an increasingly important role in pharmaceutical development, by preventing the onset of and curing previously un-curable diseases through the implementation of new diagnostic methods and treatments. Pharmaceuticals produced through biotech methods, such as proteins, antibodies, enzymes comprised 25% of pharmaceutical sales in 2003, already [6]. But most of the pharmaceuticals currently undergoing clinical trials are biotechnological in origin. The percentage of pharmaceuticals

produced using biotechnological methods, is growing rapidly. Of all registered small molecules, significantly more are produced by biotechnological methods, than by synthetic methods. (Figure 1.)

These were all changes that radically altered the perspectives and tasks of biotechnology. Main directions of research were shifted, and the map of biotechnology was rearranged by economic factors as well. Therefore these are definitely disruptive innovations. Figure 2. shows growth of biotechnological knowledge, plotted against a timeline:

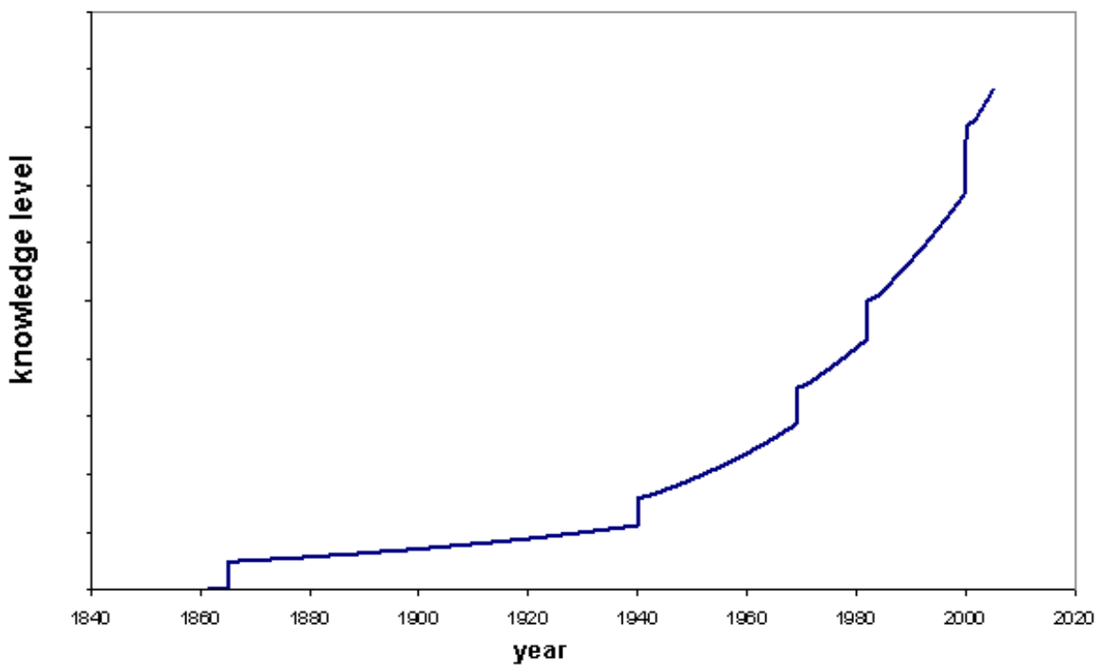

Fig. 2. [the authors]. Changes of the knowledge level in biotechnology

Usually, there is a complex, multidimensional, non-linearly correlated uncertainty surrounding disruptive, especially radical innovations, the solution of which often requires cross linked steps. It is important to state, that in terms of management, in opposition to small innovations, the management of radical innovations includes the ability to navigate in sight of unforeseeable events [1].

Biotechnology and pharmaceutical companies

Medical biotechnology is realised by two main types of companies. They are either large companies drawing on a long history in the given field and developing into more and more innovative biotechnology users, such as large pharmaceutical companies ("big pharma"). Or, modern biotechnological companies emerge, which the previously stated large companies purchase knowledge, projects or services from. Mainly the large companies control the biotechnology industry with regard to revenue. However this does not lead to strict adherence to traditions and the conservation of states of power. This is because, in terms of knowledge and the number of innovative projects, altogether small biotech companies have the comparative advantage.

Many biotech companies were founded in the 80-s. (e.g. Idec, SAFC Pharma, Enzyme Bio-Systems,Novagen). First they sought to become completely vertically integrated companies, encompassing everything from R&D to production and sales. They realised "closed innovation", only. Gradually, these companies brought new trends in their innovation strategies. At first the companies lacked two things that kept them from reaching their goals: the lack of funds, and experienced managers. However, these two things are essential (in addition to technology) for a company to grow from a spin-off enterprise to a large pharmaceutical company. The classic pharmaceutical companies, being on the top that time, already possessed these resources. Thus some of them purchased biotech companies while others however were not open to biotechnology in terms of investment and cooperation [8].

The volume and complexity of biotech and pharmaceutical projects grew in relation to the amount of available information and acquired knowledge in an environment of steadily growing needs for new knowledge. This placed further emphasis on cooperation, the sharing of costs and risks of producing new R&D results, because an industry of high risk-high benefit type emerged. This led to problems, but opportunities as well. Concerning the problems it was asked: Who will finance the costs of research? Will investors think that the industry is too risky? Naturally the significance of professional investors and specific tenders? increased with this.

Companies were forced to cooperate due to the high risk associated with biotechnology, the complexity of strategic management rules and the unusually high amount of needed funds. First of all, the necessary monetary tools are available only at the largest companies. Second, the necessary competencies are often missing with smaller companies. For example, a smaller company, a market leader in R&D, does not have the necessary experience either of the capability needed to clinical testing or production. Cooperation is necessary to fill these gaps. With this sharing of different sorts of risks will be realised. These risks, actually non-calculable uncertainties several times, may be technology, market, regulatory or competition related. The latter reflects on the segments of all the other risks, since the rapid development of China, South Korea and India. The only advantages can only be quality and knowledge for the traditional pharma producing countries. But precisely these are areas where China and India are developing rapidly, while maintaining the seemingly natural price advantage. Europe and the USA can only compete with these products if they do not count on price advantage, but on therapeutic advantage. This means producing a newer, better molecule, first of all. However this larger added intellectual value brings larger risks on behalf of technological, market and registration. These tendencies are also catalysts of cooperation.

It is precisely these different, yet interrelated risks that make pharmaceutical biotechnology complex. To successfully manage complex processes and instability necessitates cooperation. Instabilities are cross-linked, they can even strengthen or weaken each other. An example of mutual strengthening is the technological uncertainty of producing a new molecule, and the registration and legalization which follow. Registration gives the same molecule an added economical value and can, if it is registered already, decrease market instability, since it can become a market leader, a so called "blockbuster" with multi-million dollar yearly turnover.

Thus instabilities constitute a kind of synergic system. Instabilities are difficult to predict individually, their interrelations are even more so.

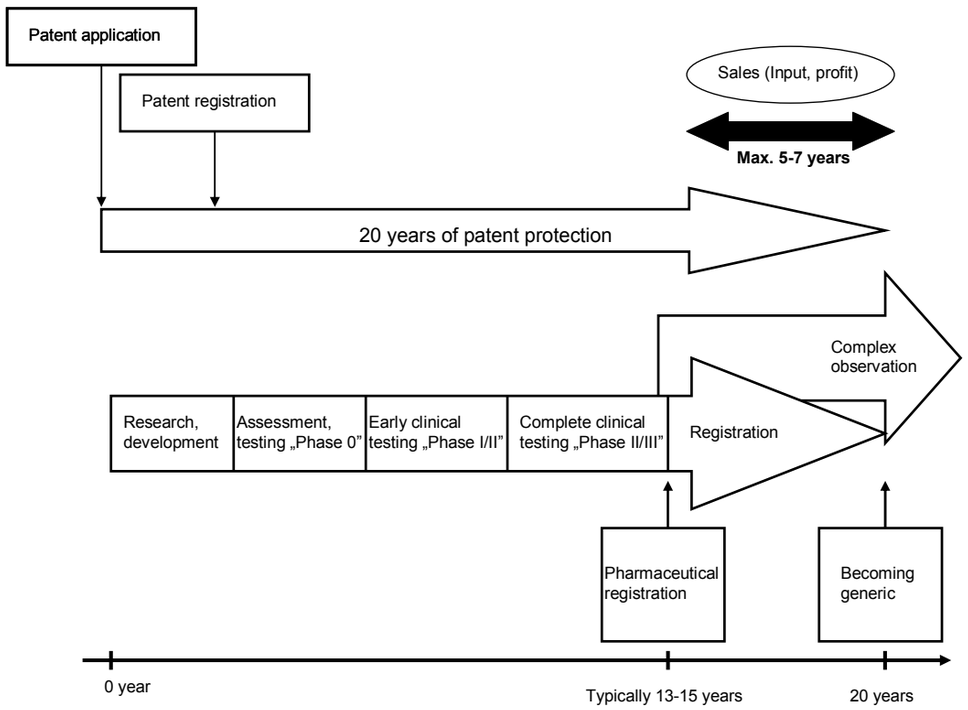

Fig. 3. [the authors]: a typical time-schedule of a new biotech identity

Necessity of cooperation can be explained from another point of view as well (figure 3). Validity period of a patent is 20 years from the date of application, which, in case of pharmaceuticals can be extended by at most 5 years (SPC). According to Figure 3, the product generally appears on the market 13-15 years after the patent application. With the end of the patent period, one must also count with the appearance of generic and biosimilar products.[2] Thus there is, at most 10, but more often only 5 years to cover the entire costs of R&D and clinical costs and make some revenue. Thus everyone seeks to make the time needed for R&D as short as possible. One method could be some sort of open innovation, which supports cooperation and outsourcing instead of solving everything in-house. /On "open innovation" you find more details in [9] and 10] /. There are numerous factors which make a part of the R&D earlier fully integrated in the vertical control target of outsourcing. To shorten the needed time to find a molecule and make it a drug, the steeply growing costs of keeping all the needed expertise within the firm, the decreasing costs of reaching the needed expertise outside, together the transaction costs arguments and the abundance of expertise outside are all for giving advantage to trust R&D tasks to outsiders who are already experts in the given field. This method definitely saves time and possibly costs as well and systematically open access to better solutions than those available in a "closed innovation" method.

[2] A **generic drug** (generic drugs, short: generics) is a drug which is produced and distributed without patent protection. The generic drug may still have a patent on the formulation but not on the active ingredient.
Biosimilars or follow-on biologics are terms used to describe officially approved new versions of innovator biopharmaceutical products, following patent expiry.

The consequences of uncertainty

Not all of the multinational drug companies had enough courage to apply the newest discoveries of biotechnology from their own budget. Obviously they regarded to these projects as they are too risky and for multinational and successful companies they didn't provide enough motivation to jeopardize their convenient state. But smaller enterprises, spin-off companies and biotechnological organizations must had to apply the new and more risky technology, which is based on new paradigm, because this was the only competitive edge for them against the big companies.

Until recently biotechnological companies have limited themselves to the early phase of the research and they sold their products, ideas and research results to drug companies. These biotechnological companies were quite small, and they had no possibilities to develop their own product as drog, only the "knowledge-import" were really achievable for them. Most of them became bankrupt, did not become successful, only some of them stayed alive after the initial phase.

Multinational drug companies often bought ready molecules from small biotechnology enterprises before or after the clinical phase II. With these purchase they could reduce their non-calculable risk attached to the uncertainties of R&D – although it stayed significant in this phase, too – but at the same time it caused success for small biotechnology enterprises. As a result new types of organizations appeared: e.g. contract manufacturing organizations (CMO) sites (contractual plant), contract research organizations CRO organizations (contractual research site), advisory and supply companies. This process can also interpret, which says that organizations share their risks similarly to their work and revenue.

So risks can be reduced thanks to cooperation and when risks are non-calculable, the precaution provides the other possible solution. The above mentioned risk reducing mechanisms suggest to apply the "open innovation" method, which can be read in details in the final document.

The four elements of the required framework highlight the key resources and dynamics associated with the emergence and sustainability of leading clusters in all segments of the biotechnology industry. First, as mentioned earlier, the development of biotechnology innovation requires access to specialized inputs, including researchers, risk capital, biological materials, and even intellectual property. By and large, accessing these resources is most easily accomplished within a regional context, rather than across long distances or political boundaries. For example, the development of the agricultural biotechnology cluster surrounding St. Louis depended on the ability of companies such as Monsanto to draw upon and reinforce the significant expertise and research capabilities of Washington University in St. Louis.

Second, a key driver of effective clustering in the biotechnology sector seems to be competition among locally based biotechnology companies. These companies compete on the basis of attracting talent, publishing high-quality scientific research, and attracting investment and interest from venture capitalists and downstream commercial partners, many of whom are located outside the cluster. This is perhaps most apparent in some of the clusters associated with health-oriented biotechnology; for example, the Massachusetts biotechnology cluster includes more than 400 different firms, 235 of which are developing therapeutic drugs [11].

Third, most leading biotechnology clusters are located not only near sources of high-quality basic research but also around areas with significant capacity in clinical innovation. For example, the pressures on the Massachusetts biotechnology cluster arise as much from the presence of demanding clinicians in the leading hospitals as from that of specialized genetics researchers. Similarly, the medical device cluster in Minneapolis is pushed by demanding consumers at the Mayo Clinic and related institutions, and industrial biotechnology innovation in Scandanavia depends in part on demanding customers in the chemical industry [12].

Finally, the biotechnology cluster depends on the presence of related and supporting industries, most notably an active venture capital industry to supply managerial expertise, risk capital, and relationship experience with downstream partners as well as key pieces of infrastructure (e.g., biological resource centers, specialized seed banks and agricultural research stations, specialized equipment and tools). Each of these factors encourages the investment of sunken assets and the development of specialized capabilities that reinforce the strength and ultimately the international competitiveness of that cluster environment.

While the United States remains the largest single national home for biotechnology activity, it is useful to note that the EU actually accounts for a greater number of companies than the United States. [13]. Along with the earlier employment statistics, this suggests that individual EU biotechnology companies have fewer employees (on average) than their U.S. counterparts. Simply put, this means that the scale of operations for a typical EU biotechnology firm is smaller than that of a biotechnology firm in the United States.

Furthermore, the European biotechnology companies seem to grow more slowly than their U.S. counterparts. By and large, young European firms are often overtaken by international competitors and even some of the oldest European biotechnology companies have been acquired by U.S. companies that have better access to financial and commercialization resources [8]. As in the employment statistics, this concentration of small companies seems to reflect the international distribution of employment activities.

This central insight—an increase in the number of regional innovation clusters, rather than a simple dispersion of biotechnology activity—holds several important implications for (1) evaluating the global biotechnology industry going forward and (2) developing effective policy to ensure continued U.S. leadership in this area.

First, some analysis suggests that the impact of globalization on biotechnology innovation seems to be different than that of traditional manufacturing sectors, such as the automobile industry or the IT sector. Specifically, the globalization of other industries reflects the increasing availability of low-cost locations to conduct activities that previously had been done in the United States. In contrast, the globalization of biotechnology reflects a "catching up" process by a small number of regions around the world that seek to compete head-to-head with leading regions in the United States.

Second, it is important to account for the range of activities now included within the biotechnology industry, including diverse applications in the life sciences, agriculture, and industry. Although most discussion focuses on life sciences—which remains the largest single segment of biotechnology in terms of employment, enterprises, investment, and patenting—the globalization of biotechnology is occurring most rapidly in industrial

applications. Moreover, although the United States continues its historical advantage in agricultural applications, this may be due to political resistance in Europe and other regions rather than the presence of strong agglomeration economies within the United States. For example, the presence of extremely strong clusters with a high level of entrepreneurship that characterizes life sciences biotechnology seems to be a bit less salient for agricultural applications. The presence of multiple industrial segments—each of which is associated with distinct locational dynamics—raises the possibility that, even as individual clusters become more important within each application area, the total number of global clusters may increase with the range of applications.

Third, at least in terms of the available data, the United States maintains a very strong, even dominant, position within biotechnology. While some conceptual frameworks (e.g., the convergence effect) would suggest that early leadership by the United States would have been followed by a more even global distribution of biotechnology innovation, the "gap" between the United States and the rest of the world has remained relatively constant over the past decade or so. Indeed, itis likely that the United States has a historic opportunity to establish a long-term position as a global hub for biotechnology innovation, particularly in the life sciences and agricultural areas. In contrast to traditional debates about outsourcing, it is possible that increased global activity in biotechnology can complement rather than substitute for U.S. investment, employment, and innovation.

Finally, our analysis highlights the small size (in terms of absolute levels of employment) of the biotechnology industry. While industries such as IT may plausibly be associated with a large impact on the total workforces of individual states and regions, total employment in biotechnology is very small, although associated with very high average wages. The simple fact is that, if the biotechnology industry remains at roughly the same scale that it has achieved over the past decade or so, it is unlikely to be a major driver of employment patterns and overall job growth, either in the United States or abroad.

Trends in the Pharmaceutical industry[3]

In terms of individual pharmaceutical trends, there are many cited novel commercial models and the rising importance of emerging markets as the most promising. Further consolidation through **Mergers, Acquisitions** and alliances and partnerships made it a close third. Difficult market access and reimbursement were named as the biggest risks, along with pricing pressure and general cost containment. Novel commercial models have been an industry issue for a while. Not only have new stakeholders, such as payors and patients, gained influence. On a different note, many managers believe that by rethinking traditional models, corporations could improve their image.

The rising importance of emerging markets is reflected by a number of developments. For example, in 2008, GlaxoSmithKline established an Emerging Markets region and appointed its President to the Corporate Executive Team. Contrary to mature markets, the middle class in such regions has increased its purchasing power. Furthermore, the public provision of healthcare is improving. Yet some stumbling blocks remain, such as the issue of liberalization in Russia or the need for better protection of intellectual property in India. However, in summary, there is no doubt that emerging markets will provide a key growth

[3] We rely in this chaper on the [14] heavily.

engine in the midto long-term. In the meantime, the BRIC countries allow the industry to learn in a "non-traditional", much more consumer-driven environment.

The challenges ahead[4]

Market access and reimbursement have emerged as top management issues. According to our survey, generating demand with physicians is no longer sufficient. This can be traced back to the increasing hurdles related to reimbursement. Hence, many managers expect that the trend, not to launch products in certain markets, will accelerate – as could already be witnessed in the UK, Germany and France.

As with reimbursement, general cost containment has also resulted in significant pricing pressure across most markets. A major driver of this development is the discounts which are granted to payors. Moreover, due to fragmented budgets and decision-making, total costs are not relevant enough: It is the price of the product which counts.

Most executives concur that R&D productivity remains a key challenge. Some are even convinced that this is the underlying issue for all of the industry's problems. For one, costs are on a steady rise. Yet, due to poor clinical trial results and higher regulatory hurdles – which have increased costs by 50% and more – the number of approvals cannot keep pace.

"The industry needs to apply a model which is less fragmented and much more entrepreneurial", said one top manager. The issue of insufficient intellectual property protection earned mixed reactions. While some managers believe that it could challenge the existence of the entire industry, others are not as pessimistic. Some pointed out that, should patent protection fail, R&D expenses could be reduced by two thirds. Others see the matter as a call for action: "The industry should stop fighting for patent protection and learn to create protected market situations using different instruments, such as brands or customer loyalty."

The industry is reviewing its commercial model. While corporations are driven by the wish to better cope with changing customer structure and become more cost-effective, they are simultaneously investing in services. At this point in time, however, this is seen as an effort to maintain customer access and loyalty, rather than as a contribution to revenue and profit.

Even in today's challenging economic environment, the pharmaceutical industry can still be considered an industry with good long-term prospects. Expanding aging populations, increased wealth in emerging markets and unmet medical needs, accompanied by rapid technological progress, are fueling the demand for innovative drugs – and will continue to do so in the future.

Product innovation and patents – formerly the driving forces behind the industry – have lost momentum. After years of high growth for shareholders in the 1980s and 90s, significant value has been destroyed since the turn of the century. The old blockbuster business model has lost its appeal. The pipeline has dried up and the number of commercially viable candidates is down. Companies show limited willingness to have a large share of their sales depend on just a few products. Health systems are challenging the highmargin business

[4] We rely in this chaper on the [15] heavily.

model of the industry, primarily by questioning the value contribution of "pseudo-innovations" and "me-too" products.

Fierce competition from generics and a growing focus on price in tender business. The first step for executives in pharmaceutical companies is to review which therapeutic areas (TAs) they are currently active in and decide whether these are really the most promising ones. What are the TAs with the highest potential in terms of revenue growth and profitability in the next five years:

- Oncology
- CNS
- Cardiovascular
- Vaccines
- Diabetes
- Immunology

For many years the typical product manufactured by the pharmaceutical industry was the pill or capsule containing small molecules surrounded by galenic technology. This has changed dramatically in recent years and more changes are on the way. We asked participants in the survey what type of physical pharma product they thought would gain most in importance in the coming five years. Here's what they said:

- Biologicals will be the strongest growth drivers in the next five years (49% of respondents)
- Combinations of pharmaceuticals and diagnostics were ranked second (30%)
- Small molecules came third (9%) – a dramatic drop in the ranking from previous years
- Cell-based therapeutics came a close fourth (7%)

This shift in product types is expected to have a major impact on the pharmaceutical value chain. Thus, pharmaceutical companies seeking approval for expensive biologicals will need to clearly demonstrate the additional benefit of their drugs in order to ensure reimbursement. Indeed, in the survey, 74% of respondents considered reimbursement and market access the biggest challenges faced in the pharma value chain. Demographic change and technological advance are driving the demand for pharmaceutical products. But most pharmaceutical companies operate in markets which are not liberalized. In such markets, prices are not the result of supply and demand but of restrictive governmental healthcare systems that limit market growth. In light of the financial crisis and the resulting large fiscal debts, growth is set to slow even further. We therefore asked the participants in our survey to name the financial source that they thought would fuel the growth of the R&D-based pharma business model in the coming five years.

The majority of respondents in the survey (78%) said that the first step would be to improve the personal or "soft" skills of their employees. Specialist expertise is also seen as major challenge by respondents working in the area of R&D. One such respondent commented as follows: "It is not only about those soft skills. You need the top people with the top specialist know-how for those TAs you want to play in." To achieve cultural excellence, pharma executives intend to focus on three levers: (1) gaining access to the best talent; (2) fostering entrepreneurship rather than bureaucracy; and (3) focusing on the

scientific culture in R&D, incentivizing employees accordingly. We will discuss each of these levers in turn below.

3. Risks and uncertainties

Calculating risk needs on the most basic level knowledge of the issues, the variables, damages or benefits, and knowledge of the occurrence of their probability. Andrew Stirling [16] elegantly demonstrates how with lessening of knowledge of the variables, that can occur as impossibility of setting just one model of the issues, because of value differences in indication what the important problem to choose is, and parallel with this, lessening knowledge of probabilities separates different areas of uncertainty.

Figure 4 shows the risk sharing process. By their nature, completely new biotechnological projects, aiming at radical innovation, originally fall into the "suicide box". They are characterized by high market and technological uncertainty. In a given situation, a small biotech company, since it has no other choice, working out the right technology, sells it to the larger pharmaceutical company. From the point of view of the big company, the technological uncertainty is reduced considerably, since it is purchasing a technology that has been proven to work. (The technology is over the proof of the concept phase) The market uncertainty remains now to solve, which can be assessed and estimated by the purchaser. Another extreme case is when a small innovative company tries to become a supplier for one of the large market players. Trying to meet its needs, perhaps even relocating closer to the purchaser, is thus reducing market uncertainty for both parties. Thus the reason for cooperation is to decrease at least one, but preferably both (marked by dashed arrow) uncertainties. By sharing the associated risks, the organizations will not be able to reach the small innovation level, as this is not the goal of the cooperation. But at least they can decrease risk somewhat.

The not always appropriate knowledge of the events causes an enormous problem for biotechnology. For example in drug manufacturing with genetically modified organisms, in comparison to traditional pharmaceuticals new problems appear, such as the social and environmental acceptance of the technology that can be doubtful. This generalized the judgement of the work with recombinant organisms, independently of the fact that the organisms are isolated when they are in use. However those "classic" events, which have influence on the behaviour of the pharmaceutical manufacturing, for example the cartel of the competitors and the status of the industrial property, have played a role yet. The appearance of biogeneric or biosimilar molecules, which generate further uncertainty (n-dimension uncertainty) in the field of regulation and licensing, is a new and not predicted problem. All this indicates that the actors in the red biotechnology are often unable to set risk calculations, first because unpredictable variables emerge, crop up.

The probabilities are the other problem. There are fields, where the probabilities can be estimated relatively easily (e.g. industrial property, technician feasibility), but elsewhere it is a really hard work (e.g. modification of regulation, variability of marketability, price or supply and demand). The latter cases cannot be generalized from the classical examples of the pharmaceutical or chemical industry, because they are biotech-specific. On the whole, there are also probabilities which can be regarded as unknowns. The most difficult thing is

to take into consideration the hazard of the unknown processes before decision. So in the case of a radical biotechnological innovation we can talk about ignorance, the field of the real surprise in the figure.

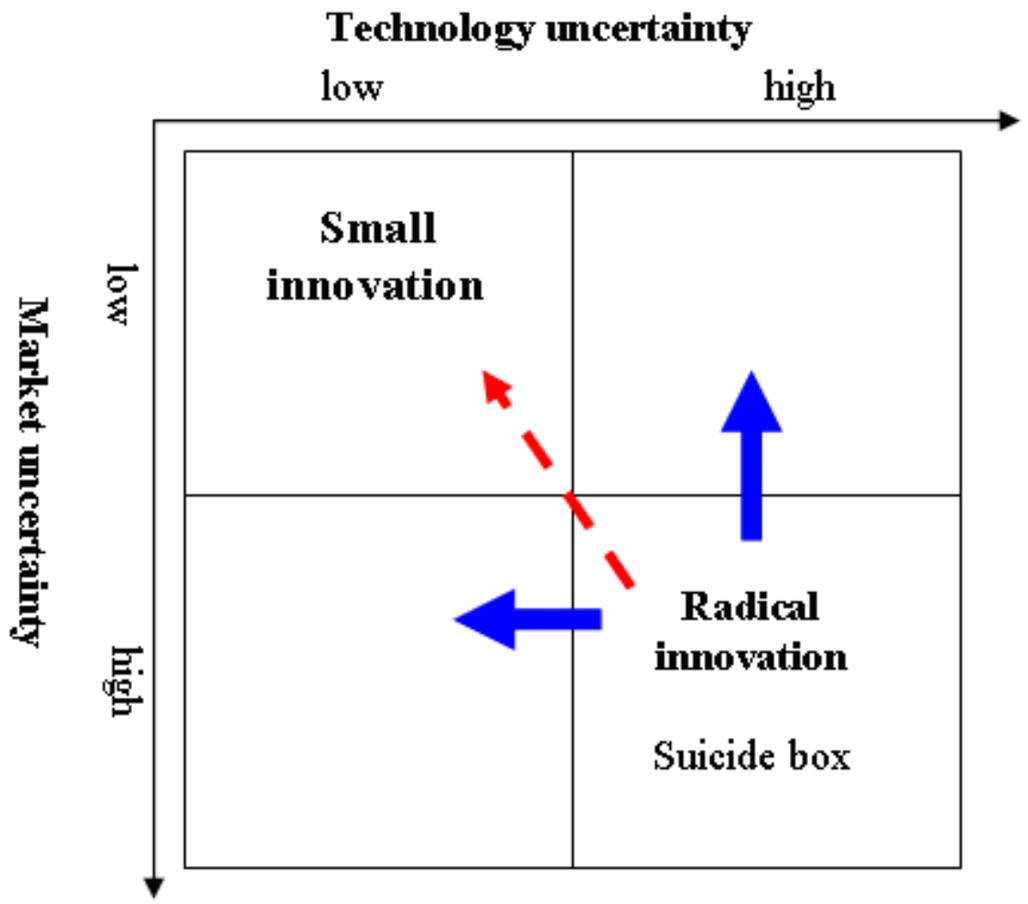

Fig. 4. The risk sharing process, based on[16] (modified by the author)

Hence we can regard that sooner or later in the field of the drastic decrease of the knowledge we can not only talk about uncertainty but its extreme case, ignorance, because we don't know or cannot know about neither the probability of the occurrence, nor the existence of the forthcoming events [17].

Breakthrough, radical innovations are created under circumstances which lead to genuine surprise. They necessarily imply essential previous ignorance, and result in genuine surprise. To different extents, this is the definition of radical innovations. That is the reason why managing radical innovation, the uncertainty and the unknown, the sphere of ignorance, has a consequence. That is that some sort of trial and error approach is a key issue, so any recognition of some, even very weak paternisation, regularity can be enormous comparative advantage. With this we acquire some plausible knowledge about a part of the "previously unknowable" while taking certain interrelations into account. It can be stated that during the evaluation of an uncertain situation partly the "I know that I know" problems should be handled. In this case a deterministic, at least a probability based answer

can be provided for. Other problems are of an "I know that I don't know" nature (I know the phenomenon but I don't know the possibility of the occurrence). In this case we can provide plausible answers. The third type is the "I don't know that I don't know" problem, meaning ignorance, already a challenge that both even events and effects are unknown. These are extreme situations e.g. when extreme security requirements are to be realised or outstandingly high profit is searched for. In permanently turbulent environments these questions become the natural questions. [18]

Two types of problems emerge in very uncertain situations. First, we literally do not know what can happen (for example by the synergistic effects of known factors and what can the effect be) and second, we do not know the frequency of what happens either. It is most important to see that the main problem with these types of issues is not the calculability with prognostic aim. The problem is the lack of knowledge what can occur at all, the so called lack of ability of modelling.

In terms of biotechnology, uncertainty in the progressing realization of some innovation can be understood more as "ignorance" or "real surprise" for a while. With the accelerating development of biotech industry the domain of "we don't know what we don't know", the range of insufficiently known events and distributions, 'original surprises' is becoming increasingly important, in most cases also accented by irreversibility [19]. Fuzzy sets considerations can only be part of the solution for these types of issues. At their border "ignorance" is impossible not to take into account if there are reasons that the turbulence is very high.

The lack of the possibility to make reliable risk calculations poses a problem. For example, when looking at the production of pharmaceuticals through genetically modified organisms, producers have been faced by problems such of the societal acceptance of the questionable health and environmental consequences of the technology. These concerns result in an overall negative judgment of all technology using recombinant organisms, regardless of their isolation during use. At the same time, "classic" events influencing pharmaceutical production still play a role, such as the merging and cooperation of concurrent companies in the background, as well as the state of industrial rights protection. A new and non-foreseeable problem is the appearance of biogeneric / biosimilar molecules, which generate further uncertainty in the fields of regulation and registration (n-th dimension uncertainty).

Based on this we can ascertain that in case of the drastic reduction of knowledge, sooner or later we can begin talking about lack of knowledge, ignorance instead of uncertainty, since we do not have, in certain cases, we cannot have any information regarding the events to come, not just the frequency of their occurrence [20]. The trivial consequence for action is than that it is wortwhile to prepare to accommodate, as a very basic element of the strategy of firms, to new situations occurring as consequences of genuine surprises.

But to provide approapriate knowledge base for any risky situation, notwithstanding that they are calculable or not, is not enough to take into account risk/uncertainty facts, only. When dealing with the role of uncertainty for decision making mostly it is too much told about the risk facts, the analytical level. To make decision, action conclusions leads to empirical fallacy, a misbelief that facts alone can lead to decisions. But decision making unavoidably includes risk evaluation too. It is unfortunate that the risk assessment literature

neglects this layer.Actually, it is a hidden assumption that everybody naturally makes the same evaluation of the same facts but this is a simple error. Following Schwartz and Thompson, and utilizing ideas from lectures of Imre Hronszky and the PhD Dissertation of Ágnes Fésüs we shortly demonstrate what with risk evaluation the issue is. Actually at risk evaluation for basic types of evaluating perspectives can be utilized. The Figure 5 below demonstrates them.

Types of nature represented by different potential curves accepted by the four different types of agents in society, according to Schwarz and Thompson:

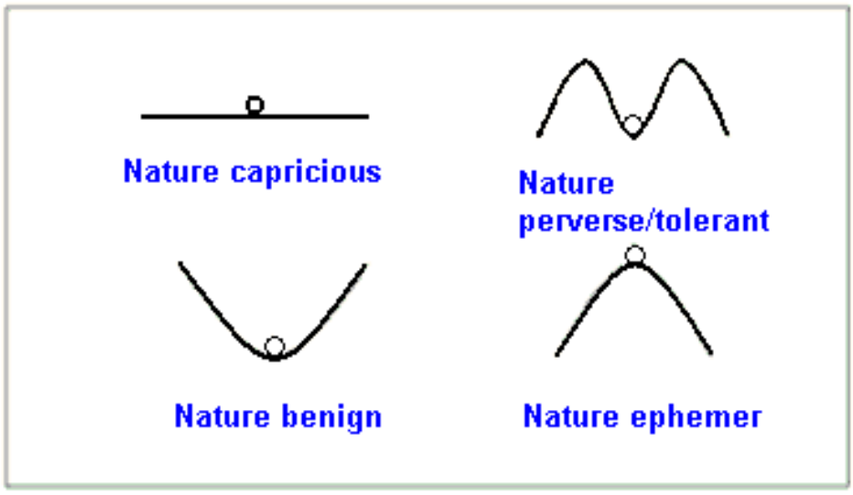

Fig. 5. Four different types of agents in society, by Schwarz and Thompson based on [17]

On risks and uncertainties

The assessment of risks (uncertainties) in the technological development is becoming an increasingly difficult task to solve. This is especially true in a rapidly changing turbulent environment, where environment and its knowledge changes from day to day, where in addition to small ones, radical innovations are typical as well. Understanding the necessary parameters is becoming more and more uncertain, thus also becoming limited. There is a huge literature on technological uncertainty just as there is on risks of financial issues.

Two types of problems emerge in very uncertain situations. First, we literally do not know what can happen (for example by the synergistic effects of known factors and what can the effect be) and second, we do not know the frequency of what happens either. It is most important to see that the main problem with these types of issues is not the calculability with prognostic aim. The problem is the lack of knowledge what can occur at all, the so called lack of ability of modelling.

The classical scientific assessment of uncertainty is the quantitative risk assessment (qRA). If you know the damaging events and their frequencies you certainly can make prognostic calculations, too. QRA has a quite long success story in modernity. But, for its reductive nature, that we have to know these very basic preconditions, it is with ignorance ('deep uncertainty') hopelessly challenged in strongly turbulent issues and with basic lacks in knowledge. These types of problems will be more and more often.

Understanding uncertainty in modernity has developed as a progressing capability of calculation of risks, the quantitative risk assessment (qRA). As its essential it is calculation of the probabilities of occurrence of some known set of events and multiplying these probabilities with the possible damages the set of events may cause. This way the qRA aims at the best possible prediction of risks. This approach includes into the (probabilistic) deterministic planning and command and control regulatory approach. All these issues, qRA, deterministic planning, command and control approaches require the existence of quite strong preconditions (as, concerning qRA I indicated above). These strong preconditions can up to a grade be weakened. For example fuzzy set techniques can be included concerning the estimations of events.

It is important to see at least in outline how uncertainty of events and likelihoods and the plurality of the values as a societal fact for democracies have challenged the modernist approach to uncertainty. Andy Stirling, in line with some other authors, elegantly summarizes the basic problematic of quantitative risk approach as providing for a reductive-aggregative way to interpreting uncertainty [20]. One can speak about reductivity in the meaning that the classical risk research reduces its interest in calculable risk. This could be done, concerning the production dimension, in time of mass production. Then long periods were stable and made the prognostic effort rather successful. We can make rational suppositions on the basic preconditions of risk calculation in such periods. Additionally, a lot of efforts have been made by practitioners in risk research to find methods to successfully assess situations when quantitative risk calculation ceases to work exactly. This applies both for making conjectures about the existence of events as well as their probabilities.

It is just a platitude to say that knowledge in any real case is incomplete in most decision situations. Important is what sorts of incompleteness are or/and are to be recognized. From the quantitative risk perspective, to be able to function, we should be able to identify the events that should be taken into account and should be able to attribute values to probabilities at least as subjective guesses. But one can also consider a further case when this does not work with either the events or the probabilities. Instead the earlier cases even strong 'surprises' may occur. History helps us to learn on empirical base that these sorts of cases, issues and effects of 'unknown unknowns' are real cases. These can occur without any human interaction or as results of them. It is possible to argue that high complexity of the issues provides for frequent occurrence of 'surprises'. All the radical innovations are in their realisation process for a while 'surprises', too.

On the precautionary approach

All this is connected to some recognition of the nature of uncertainty of the processes and the appropriate management efforts. The new permanent and decisive challenges are decision making and action under the pressure of comprehensive and irreparable information uncertainty in a world of 'ontological uncertainties', as this is typically formulated.

Risk management based on quantitative risk assessment does not help much in these issues. The reason is that both the needed type of assessment and the controllability of the process too are realisable in a limited way only. Risk assessment has to draw back to the second line, to the efforts made for isolation and control of special issues. But this should not open the

way to nihilism. Instead, some sort of precautionary approach is possible to unify as we try to emphasize the commitment of the actor both for utilising suddenly appearing chances and avoiding hazards. While risk calculation, the extension of the calculative rationality attitude to uncertain situations, in principle promised the certainty of exact calculation of the one best solution (in an ideal world where neither the unavoidable multiplicity of values, the 'combinatorial complexity' neither real complexity disturbs) rational management of complex processes has to be satisfied with calculations unavoidably leaving essential place for uncertainty. This is where value choices have their structural place. With this we already want to call attention to the issue that it is reasonable to think of a continuum of approaches, made of different combinations of courage and drawing back. This continuum of behaviour reflects the variability of human agents' relation to the uncertainty as a world of chance and hazard.

Modernity first had success with mathematically handling deterministic issues. Then it went further and had immense success in handling probabilistically deterministic issues. As its pair in management caution and prevention may be seen as key categories developed by modernity in relation to mastering negative effects. This is mastering by and preventing based on (in principle exact) understanding of the probability of causal mechanisms. In this latter case it is risk that comprises the relation of modernity to uncertainty: uncertainty can in principle be bounded in exact calculus. As for exchange there is no place for surprise in issues where quantitative risk assessment is valid, as Frank Knight sharply recognized in 1916. This is to set against a 'post'-modern 'world' in which interactions and 'deep uncertainty' assessments get the supreme position. The realised rationality by modernity is calculation of isolated issues as exactly as it can be done, with the result of possible exact prediction of the effects. Its action part is to come to term with the outcomes the probabilities of which are calculated. This rationality of more and more exact calculation is the basis for acting through deterministically planning that is based on evaluating the realisability of probabilistically predicted positive and avoidability of the negative effects. It is oriented toward exactness in quantity. That means that the methodological effort can concentrate on identifying the degree of risk. Concerning the future, this open space of unknown, risk calculation commits itself to understand future through extrapolation based on some continuity. Estimated uncertainties in the future are compared with the known risks recently and these are hypothetically extended to trends into the future. (With this there is a, not always conscientious reductive presumption made on the type and 'measure' of novelty. Because the induction problem is unsolvable in principle trend extrapolation has to be decisionistically accepted. It will or won't be rejected. At some point we do not reject anymore as Bernstein [20] correctly recognized the extrapolative guess as measure for what can be novel in the future. There are two different basic types of practices to realise this non-rejection. We may make it because it is acceptable for modelling or for practical reasons in the real practice.)

Risks appear this way as if they were quasi-natural variables, objective, repeatable, and measurable in standardised situations. But we know that risks are social-natural variables, damages are damages in relation to some values, only. So, even when they seem to be quasi-natural variables, a justified multiplicity of risks can be identified around the same issue, expressing the (often conflicting) relations of interested groups to the risky issue. This is the mentioned ambiguity of the valuing relation. Life is obviously more complex than any of the

leading ideas on which actions can be based on their purified forms. Modernity also experienced that values are irreducibly multiple in democratic societies and that uncertainties around the data and the models definitely hinder the unambiguity quantitative exactness risk management in its ideal form requires. The unceasable value plurality, as characteristic for the manifoldness of the social processes and a democratic society together is a strong challenge to classical risk assessment. It challenges at least its claimed punctual exactness, its capability to provide for any unique 'objective standard' for decision making. Risk assessment is unavoidably based on some 'subjective' framing. From the endless many perspectives one will be chosen to serve for realising a qRA process. One has further to see that risk is not only social-natural variable because it expresses a special evaluative relation (damage) to some object but risk is also constructed in reality: one can rightfully, strictly speak of quantitative risks of an action in standardized systems, only. So, either the situation is really standardised as far as possible in the real practice or is identified so as it really would be standardised.

4. Conlusion

Pharmaceuticals is a highly globalized industry, dominated by multinational companies that engage in significant business activity in many countries and whose products are distributed and marketed worldwide. Historically, the industry has been dominated by vertically integrated firms performing almost all of the activities in the value chain by the firm itself, from basic research through to sales and marketing. They realised some sort of "closed innovation", as Henry Chesbrough introduced the term. [12]

In recent decades the industry has undergone dramatic structural changes, with the rise of the biotechnology sector, substantial growth in demand driven by demographics, substitution away from other therapeutic modalities such as surgery, and increased competition from globally active generic manufacturers

Pharmaceutical biotechnology, just like other dynamically growing branches of industry, has been very rapidly changing. Disruptive innovations arise from time to time. Since this is a very high risk - high benefit industry, and already R&D phases often require several hundred millions of dollars, the participants seek to minimize and share risk, more precisely the uncertainties, not always calculable as quantitative risks.

In case of biotechnology the assessment of risks (uncertainties) in the technological development is becoming an increasingly difficult task to solve. This is especially true in a rapidly changing turbulent societal, economic, political, ideological environment, where that environment and knowledge of it changes from day to day, where, in addition to small ones, radical innovations are not seldom but typical as well. Understanding the necessary parameters is becoming more and more uncertain, thus also becoming profoundly limited, just as with the whole dynamics.

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It is widely accepted that technology is one of the forces driving economic growth. Although more and more new technologies have emerged, various evidence shows that their performances were not as high as expected. In both academia and practice, there are still many questions about what technologies to adopt and how to manage these technologies. The 15 articles in this book aim to look into these questions. There are quite many features in this book. Firstly, the articles are from both developed countries and developing countries in Asia, Africa and South and Middle America. Secondly, the articles cover a wide range of industries including telecommunication, sanitation, healthcare, entertainment, education, manufacturing, and financial. Thirdly, the analytical approaches are multi-disciplinary, ranging from mathematical, economic, analytical, empirical and strategic. Finally, the articles study both public and private organizations, including the service industry, manufacturing industry, and governmental organizations. Given its wide coverage and multi-disciplines, the book may be useful for both academic research and practical management.

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