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# Expectations and visions in industrial practice

## On the case of modern biopharmaceutics

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### Abstract

Expectations and visions play an essential role in building strategic intelligence. They give orientation in the dynamics of sciences, technologies, and industries. Investigation of these frames of mind is rapidly expanding, with many important results. Pharmaceutics has always been an innovative industry. Biotechnology is identified as having an immense potential for an industrial revolution that also revolutionizes pharmaceutics. Concerning R&D, the essential problem of the recently converging pharmaceutics and biotechnology is the innovation of innovation. This means that the search for innovation itself is awaiting a Schumpeterian creative destruction. History of modern biotechnology is a steady stream of spectacular visions of repeated revolutions. But the realised profound progress in R&D in the process of convergence have not diminished the strong tension of the increased challenges and the permanent productivity crisis of pharmaceutics which has become chronic in the past twenty years.

This article first reconstructs the dynamics of pharmaceutics, with its central focus on ongoing blockbuster production, in which repeatedly radical expectations and visions are necessarily constructed, and have a key function. Among the players in the arena, advisory firms are of particular importance in providing strategic expectations and visions. This article investigates examples of advice that are based on forecasts of alleged revolutions in biopharmaceutics. In the dynamic tension of three components – first, the steady, extremely upgraded requirements the industry is constantly confronted with; second, its real continuing underperformance in meeting them; and third, the repeatedly emerging revolutionary potentials, first of all in molecular-biological research – an extremely stretched dynamics is identified, in which the visions and announcements of on duty "revolutions" in biopharmaceutics move from one self-suggestion to another.

## 1 Introduction

Expectation and vision-construction is integrative to any human activity. They are essential formative constituents in the various industrial practices, too.[1] We need visions, both strategic and operative, to assess how promissory technologies can realise their potentials and avoid adverse effects.

A strong research trend has been developing in the past twenty years, especially in the last decade providing a socio-cognitive interpretation for this activity (van Lente 1993, Brown and Michael 2003, Berkhout 2006, Borup et al. 2006, Kraft and Rothman 2008, Konrad 2010, Rip 2011, Bakker 2011 to name but a few authors and publications). Concerning the mechanisms of expectation dynamics, there have already been

- numerous results of reconstruction and analysis of the hype-cycle, the circulation of expectations in expectation-arenas or
- concrete analyses how guiding visions work in transition management.

The sociological approach to exploring the structural roles of expectations and visions in the abovementioned dynamics is an essential contribution. However, sometimes this is done in a sociologizing-reductionist way. Accordingly, only the sociological factors are considered when the acceptance/ rejection of an expectation/ vision is at stake. But, the dynamics of vision-making necessarily has to involve epistemological considerations. Expectations are to be made credible as reasoned narratives for scientists, entrepreneurs, governmental players. Vision-making is a socio-cognitive act, and so it is necessarily also an object of epistemological, better to say, of a socio-epistemological critique.

This article is an attempt at clarifying some sorts of expectations that have been constituent in modern biopharmaceutics in its already some decades-long history.[2] These expectations are formulated by advisory firms as visions of consecutive revolutions. The revolution-metaphor is already quasi-natural in narratives on biopharmaceutics, but is only partially correct. Obviously, there is a set of issues on the supply side which provides for a basis for narratives of revolutions, and there is a constant need for promising revolutionary solutions for problems on the demand side, namely industry. One central question is: why and how do biopharmaceutics' dynamics constantly enable and simultaneously demand devising visions of revolutions?

The article first attempts to reconstruct, at least partly, the dynamics of pharmaceutics and biotechnology (biopharmaceutics) that have been urging the conceptualisation of the future in terms of coming revolutions. Second, it turns to a specific type of players in the pharmaceutical and biotechnological arena. These are business consultancy firms such as PriceWaterhouseCoopers (PwC). As for examples, the article investigates forecasts PwC and another advisory firm, BCG, made. Third, it reflects on the narrative of science-based business (Gary Pisano's reconstruction of biotechnology) and its yield for normative requests on studying the future of biotechnology.

[1] Adam Hedgecoe and Paul Martin write in 2003: "Understanding the formation, mobilization and shape of these expectations or 'visions' is […] central to the analysis of an emerging biotechnology." (328).

[2] Most authors "abbreviate", and use the term biotechnology for red biotechnology, the utilisation of biotechnology in medicine. I prefer to use the term biopharmaceutics here, and use it only narrowly, because I do not treat medical instrument and diagnostics development. But I sometimes use the term biotechnology or biotech as equivalents.

## 2 On Vision-making and the Dynamics of the Biopharmaceutics Industry

Historical development of modern biopharmaceutics, starting with exploiting recombination DNA techniques and later including the utilisation of genomics for biopharmaceutics, realised numerous breakthroughs in many different respects. For a short while, successful biopharmaceutical entrepreneurs got the opportunity to gain wealth overnight (a hope that is already history, but reappears as a dream). These are important ingredients of impression-building.

Talking of revolutions, in biotechnology as a whole, or of methodological or organizational revolutions, mostly designates rapid qualitative changes, breaks with profound transformative capacities in their environment. Talking of revolutions can be made differently. The revolutionary narratives in biopharmaceutics refer to basic challenges, or to enormously growing menaces, heading for a crash, or basic changes of direction in research or doing business, or to the possibility of immense growth in performative capacity, or to the army of hindrances to overcome and the violence, which is an inevitable part of their realisation. To speak about a short time interval in which the transformation is to or has to occur is an ingredient of all of the revolutionary narratives; they speak about upheavals. It is important to see that all the revolutionary narratives I am dealing with here, are forecasting efforts.

Four stylized facts form the background for reconstructing the dynamics of expectations:

- ongoing repeated leaps in the development of most different constituents of the dynamics, a series of micro-revolutions,
- biopharmaceutics' evolutionary path,
- the continuing "productivity crisis" in pharmaceutics
- and the only half-successful organizational and business structures in biopharmaceuticals' dynamics.

The ongoing tension between repeated, even accelerating breakthroughs, bigger and bigger on the supply side, science, and the steadily deepening tension with the productivity crisis make the very basic problem to explain. In connection to this, history of biopharmaceutics is a story in which reality repeatedly lagged behind the often-extreme expectations expressed by different agents in the arena, but these expectations were an integral part of the real developments.

The dynamics of biopharmaceutics has both steadily enabled and urged strategic vision-making[3] both on the supply and on the demand side, aiming at catching sight of decisive breakthroughs.[4] In comparison with other branches of industry, beside ICT, biopharmaceutics provides an extremely fertile soil for radical vision-making. Immense potentials emerge from time to time and immense constraints repeatedly de-

[3] I think it is important to free the term "strategic vision" from its "obligatory" connotation of "long-term". That worked well for dynamics in which long-stable processes were changed by consecutive long-stable processes. But in dynamics in constant flux, as is the case with biopharmaceuticals, "strategic" means the ability to accommodate sustainably to the series of "capricious" processes, contribute to direction changes or other non-linearities in the environment by repeated modulating actions (Rip 2011) as quickly as possible, and keep the new direction exactly until it seems sustainable. Kraft and Rothman (2008) aptly point to Celera's repeated rapid strategic accommodations, the private genomics firm that successfully challenged the governmental human genome programme (HGP) earlier, by twice changing its profile in five years. repeatedly answering to the changing credibility of different strategic visions.

[4] Using the terms supply and demand is a simplification of the processes in an increasingly complicated networked dynamic of them.

mand exploring expected "revolutionary" potentials, taking part in producing and realizing them in an increasingly networked dynamics. These visions refer to most different content, space and time variables, and extend from overarching visions related to the industrial sector as a whole to visions of the role of new methods in development or of concrete, successful drug candidates.

Making visions workable for action presupposes road-mapping and has to find signals of progress. First successes can serve as signals for the expected bright future. Concerning their role, recognitions of signals may, for a while, provide some pseudo-certainty on how to continue or change the activity.[5] Unavoidable speculations on possible futures made by experts regularly work for science or technology management and policies, as "scientifically established rational prognoses", having the (partly alleged) authority of expertise. Advisory firms also acquired this form and level of authority.

Visions enter a "market of expectations" and acquire some perceived value pricing in negotiations over their realisability. They can assist in the acquisition of funding, or of any other resources needed. They participate in the complex processes often leading to bubbles. They can express self-confidence as at the inception of modern biotechnology, or just the opposite, be an attempt at bridging a lack of self-confidence, in extreme cases, desperation, by insisting on the existence of and pointing to the alleged certain way to the Promised Land. Sometimes, the sustained belief in the coming revolution of biopharmaceutics as a whole, the durable solution of the productivity crisis makes constrained shifts from one target to another in time, and brings about continuity in some respect: the repeated renewal of revolutionary visions pit some backbone into the activity, by preserving the faith, after consecutive failures, that looking for revolutionary solutions is the correct method to follow. Prognoses in biotechnology consecutively turn from one element of practice to another and insist on making visions that partial breakthroughs and their synergies are on the way to unify into some overarching revolution.

The serendipity factor, due to the enormous complexity of the target and in relation to it the missing knowledge, so typical for the pharmaceutical industry earlier, continues to affect its dynamics essentially in modern biopharmaceutics, but on a different level and smaller magnitude.[6]

Modern medical biotechnology reached a new level by deepening the understanding of diseases and effects of drugs on molecular level. Nevertheless, the still dominant, ontologically reductionist, genetic causal approach, by short cutting the process of catching the complexity, distorts the rationalization of the progress in drug production. It seems there is still a dominant tendency among genomics researchers to underestimate the high complexity of the tasks of understanding diseases, on three levels, the genomic, the body level and the level of the natural and social environment and their interactions. This joins the missing readiness to assess the difficulties with "unknown knowns" too. Bypassing considerations of possible "unknown unknowns" is sometimes associated with the lack of considerations of "unknown knowns",[7] as if

[5] While some of them may prove to be real signs, if only post festum, so to say, the situations in biopharmaceutics often proved to be pseudo-signs, just as lines of Sargasso did for Columbus' sailors.

[6] The earlier belt-and-braces strategy, dominant in the research based on organic chemistry, changed in research in biotech to making a smaller number of key trials.

[7] Something we know but suppress, or commit to forgetfulness is an "unknown known".

taking them into account could really be avoided.[8]

When the dynamics involve high-risk/high-benefit possibilities, actually a very high level of incalculable uncertainty, as is the case with many issues in biopharmaceutics, and some main risk problems may turn out to be solved, by breakthroughs as predictable successes of enormous and long efforts or sometimes unexpectedly, this may trigger strong hypes on sudden further breakthroughs as a result. Those agents, who believe to have been awoken in time, may hope to exploit the new situation disproportionately high. Extremely high risking may become desirable then. If multiple agents exist, their simultaneous action may result in a strong amplifying effect. But the players in the biotechnology arena seem to learn a bit as it was with the quick bursting of the genomic bubble in 2001 or is with the enduring weakening readiness to believe in sudden breakthroughs in the recent phase of history biopharmaceutics.

Signals, for selected receivers, may seem to multiply for quite a long time by progress in some expected direction. For example, the successes with one-gene-one-disease generalizations did their work, as over-generalizations for a while. And, for a while, readiness to over-generalization, encouraged by reductionist thinking, helps to sustain the idea of revolution, of the great breakthrough-in-the-making, but by referring to more resources and time needed to realise the imagined.

## 3 Revolving around blockbuster production

A short outline of the history of modern pharmaceutics, including its gradual convergence with modern biopharmaceutics, will promote understanding of the mechanisms in which the steadily renewing radical expectations are active constituents. These expectations are results of the interplay of urgent needs for radical improvements on the demand side and certain enabling breakthroughs on the supply side.

Pharmaceutics became an icon of innovative industry in the second half of the 20th century. First, it mostly concentrated on exploring and exploiting the organic chemical paradigm. Notwithstanding the constant and growing utilization of chemical and other scientific knowledge, this paradigm remained rather an empirical trial-and-error mode of research. It was backed by some theoretical knowledge, but finding drug candidates depended strongly on serendipity. Pharmaceutical research was not only a very uncertain undertaking, but also steadily required enormous investments along the whole value chain, the return on which took a rather long time in comparison with most other branches of industry. (The value "chain" takes 10–15 years from a research idea to drug approval.) The numerous repeated successes that made sustained growth possible needed the steady growth of financing, and the constant, even growing demand, the somehow sustained readiness of payors to pay more for new drugs made pharmaceutics one of the most

[8] I give an example of a preliminary bypassing of some "unknown-knowns" from the research problems of the so-called hydrogen economy. Envisioning the success of the hydrogen driven car is made by bypassing the problem that three ways are to try to solve the problem of storage of hydrogen in cars and all of them seems inappropriate to find an efficient solution. But the failure would be disastrous for the whole hydrogen car economy. The so-called "roadmap" of the hydrogen economy entails numerous problems of similar type. By bypassing the knowledge gap concerning "unknown knowns", the vision could acquire a preliminary rational status, because the "unknown-known" is swept under the carpet, as if we could be certain to be able to find a solution, even more, to find it when it is needed. Sometimes in history of technology a solution to such sorts of problem was suddenly fund unexpectedly.

profitable branches of industry during the second half of the 20th century.

The main reasons for its basic dependence on accidental factors, on serendipity in empirical research include the immense lack of knowledge concerning possible druggable targets (until quite recently), and of the mechanism of the drugs' (drug candidates') effects on the human organism, especially concerning adverse effects. But producing pharmaceuticals grew into a huge, sustainable growing industry essentially depending on R&D in the second half of the 20th century. Basic characteristics of its value chain are still the same: it is a sequentialized linear manner of promoting valuation and realization – now with ever stronger feedback from marketing or from the drug approval process, and so realising a half-linear development chain as a basic type of innovation of innovation.

Typical for pharmaceuticals are the very high costs, the very long term of return on revenue, the very short duration of patent protection on drugs already on the market, just some years, and the very high risks, including the highly incalculable uncertainty, of its R&D, the clinical trials, and the licensing process. It is quite natural that it has always been a central issue for Big Pharma (the largest pharmaceutical firms) to improve the prognostic ability, reduce costs, shorten the period needed for value realization, and, of course, trying to let prolong patent protection – the latter to weaken the serious menace of generics after patent expiration. One of the pharmaceutical industry's main recent activities is permanently to try to improve radically all segments of R&D and to change the linear value chain, even to transforming it profoundly through parallelisation and by realising feedbacks between the segments.

It is to stress that pharma's R&D has always been extremely risky and became even riskier with flight of time. On the other hand, there is the extraordinarily high profit, provided a firm could durably bring a blockbuster drug onto the market.[9] Notwithstanding the interaction of all those unfavourable factors mentioned above, modern pharmaceutics have been able to produce double-digit rates of revenue sustainably.

Blockbuster production made industry concentrate on drugs good enough for as many patients as possible. These drugs are typically on a mediocre level, concerning their effectivity and efficiency. To utilise the advantages of economies of scale and scope, pharmaceutical production aimed at realizing a steadily-expanding mass production in the second half of 20th century, which was combined with very aggressive marketing.[10]

The very high costs with all the uncertainties, and the long span of the time from research to bringing the product onto the market, with the menace of competitively-priced generics entering the market immediately after a patent has expired, prompted the firms to pursue a particular type of vertical integration and

[9] A blockbuster drug is a drug generating more than $1 billion of revenue for its manufacturer each year. A mega-blockbuster generates more than $5 billion each year. They bring the "big benefit". On the other hand, any failure in the late phase of the value chain may lead to real shakes. Pfizer lost 25% of its stock value overnight when it had to withdraw Torcetrapib, a drug developed to treat elevated cholesterol levels, in early December 2006.

[10] The "one size fits all" principle is extremely problematic in mass production of drugs, first of all, because of their possible adverse effects. Probability of possible adverse effects rapidly grows with the quantity of drugs produced, with the number of patients using them. But the production of blockbusters aims at as extensive mass production as possible. Producing pharmaceutical blockbusters is a type of mass production in which extremely high quality standard requirements are set concerning exclusion of possible adverse effects.

a particular behaviour in competition – actually, pure rivalry for a long time. Large firms implemented vertical integration, including the R&D department, but more and more complemented it by some stable horizontal co-operation, realizing a growth in division of labour by outsourcing.

Quite different is the emerging new type of collaboration in joint development of the knowledge base in recent pharmaceutics, where sharing knowledge is intended. While vertically integrated large firms were in pure rivalry for a long time, a collaboration of "new best friends" has emerged by now, along the whole value chain, not only precompetitive collaboration, to be able to stand in the further strengthening globalizing competition.[11] This has much to do with acquired learning about the nature of biotechnology, in terms of renewing the business model.

The search for blockbusters is a self-inducing, under-performing, and highly uncertain dynamics. To sustain blockbuster production under quickly impeding conditions needs a permanent striving after renewal of the big firms. This adds to the explanation of the wave of mergers and acquisitions (M&As) around the turn of the century, The extraordinary strong striving after repeated renewals in very short time applies to R&D, too. While pharmaceutics was an icon of R&D-based industry already in the beginning of the second half of the 20th century, it is by now an example of an industry in constant need of the innovation of innovation too, of permanent efforts to radically renew innovation of innovation itself. The strong interaction of the abovementioned factors led to a race that constrained and enabled a special virtuous circularity as a gradually entrenched trend. It led to intensifying path dependence and a lock-in for the industrial sector as a whole. Long before a new level had been reached, this cemented dynamics demands searching for a further radical window of opportunity for sustaining, even possibly increasing the high revenue.

A rather inflexible arena was set by the permanently tense interaction of firms, the government, and regulatory agencies, etc., partly based on sustaining diametrically different attitudes. The "rules of the game" that had been constructed by the interaction of the players provided for a rather inflexible structure. The constraint to find new blockbusters in time provided for enormously growing risks for the companies. They had to try to win or had to risk disappearing from the arena in the permanently intensifying rivalry. But constructing blockbusters can only be attempted with a few candidates in the later phases of R&D, mostly because of the enormous costs and the massive uncertainty in the clinical and approval phase. There is a steady menace of loosing the whole competition in the last step, by refusal of approval, not to speak of the compelled withdrawal of an already licensed drug. [12]

This dynamics favours large concerns. As a self-inducing mechanism, searching for blockbusters requires, for the potential of a continual renewal in terms of new breakthroughs, that potential breakthroughs are already developed while the earlier blockbuster is still profitable. This process constantly presupposes having new candidates "in the pipeline" in the right time when the predecessor's patent expires. This

[11] PwC's "Biotech reinvented" report names in 2010 some "new best friends" in pharmaceutics as ideals. (PwC 2010: 11)

[12] If you live by the blockbuster, there will be a disaster when the blockbuster fails to materialize. But developments from 2007 on show that Big Pharma is still rather locked in, and can not simply leave the path it has been following so long, even if it would be more forcefully compelled to do so as it is now.

became the first basic requirement for R&D in the growth of Big Pharma.

The pipelines started to "dry out" from the early 1990s at the latest. This happened even though, in the meantime, investments in R&D had been enormously grown. This unsuccessful attempt at solving the pipeline problem by financing the steeply-rising costs of R&D, that were felt rather unbearable by the millennium, amplified the basic problem, and sent a strong signal that, instead of simply further raising the financing, radically new means of solving it had to be found. A permanent "productivity crisis" arose in the entire branch, including drug research in medical biotechnology, because even here "the low hanging fruits had already been picked" by the end of the 20th century.

These characteristics are of fundamental importance for understanding the dynamics of the permanent need for devising radical expectations and visions on the supply side, to satisfy the radical demands. Any possible or real scientific or organizational breakthrough, such as overarching informatization, was then interrogated for its potential of causing breakthrough by solving the radical needs on the demand side of the industry. The need for innovation of innovation was widespread by the turn of the century in the meaning of profoundly transforming the way in which pharmaceutics moved and a profound turn to biotech offering arising genomics was an overarching vision.

Many industrial researchers and leaders uninterruptedly tried to catch the glimpse of the "light" from new real or expected scientific or organizational breakthroughs. One, most important enduring aspiration aimed at radically renewing the innovation chain, another, interdependently with the former, the genomization of drug research.

I jump for a second to the results. Soaring visions of promises and, especially concerning informatization and genomization, many partial breakthroughs have been realised in the last 15 years. But, concerning the problem of the solution of the productivity crisis, there has been no increase in the number of new blockbusters made yearly in the last 15 years.

The other enduring basic challenge, deriving from the reached level of the competition in pharmaceutics, can only be paradoxically solved: when one new level was reached it demanded further efforts repeatedly, in an earlier unknown measure. This characteristic irregularly periodizes the process of the growth of pharmaceutics into successive qualitative transformations, possibly requiring revolutionary breakthroughs, with every possible effort to shorten periods of equilibrium.

Big Pharma can still be defined as a group of firms which survive because they are sustainably able to successfully meet the challenge of a constant search for new blockbusters. While the costs of finding new drugs had always been rising earlier in the century, the costs of looking for blockbusters began to rise exponentially in the last decade of the 20th century. On the other hand, more and more Big Pharma firms developed connections with the new biotechnology firms. These concentrated on niche development first. Big Pharma interacted with biotech firms through different forms of cooperation in history, but especially by taking over biotech start-ups. It became increasingly clear that pharmaceutical biotechnology had to take over the task of providing new blockbuster candidates.

There seems to be a basic contradiction within Big Pharma's dynamics. From the early 60s on, it attained a decisive comparative advantage over the small firms in the drug approval regulations. This enduring advantage made them rather inflexible in many respects, but they had to adapt to the

dynamics constantly in flux that they themselves partly produced.

It seems, the main present solution is still to retain the blockbuster model on the leading place but enforce the help of biopharmaceutics, more and more looking there for new candidates. The race for blockbusters has been continued, with biopharmaceuticals forging ahead. But a new PwC report made the disenchanting conclusion in 2011:

"Pharma's strategy on placing bit bets on a few molecules, promoting them heavily and turning them into blockbusters worked well for many years, but its R&D productivity has now plummeted and the environment's changing." (PwC 2011: 3)

## 4 Biopharmaceutics on the long way of taking the lead

Since the early 1950s, the rapidly-developing disciplines of modern biochemistry and molecular biology naturally fed a vision of a new potential to realise a most profound paradigm change in drug research. This revolution in biochemistry and molecular biology provided the emerging industry with a broad scientific overview as a starting-point for understanding the mechanisms of diseases, on the level of molecular processes. By the mid-1970s, it also led to immediately-utilizable, powerful technological instruments, first through utilizing DNA recombination, and transformed bacteria to produce the first modern biopharmaceuticals.

The radical renewal in the pharmaceutical industry's R&D based on a new, molecular-biological basis was recently made in interaction with a new long-term expectation. Genetic techniques were dominantly interpreted as promises to transform R&D into a rational method, based on the development of the theory providing predictability and powerful technological instruments of earlier far not known capability. A fantastic perspective on a possible new world could be developed and helped the imagination soar. The promise of new experimentation techniques and the subsequent theoretical development to take the world by storm could work and led to exaggerated extrapolations. This could be done, provided you abandoned the profound critique coming from different corners, for example from systems biology on one hand, or knowledge of historical breakthroughs in industry on the other. If you took the narrow, reductionist perspective, the initial techniques would provide for the first unbelievable demonstrations for extrapolations, think, as an icon, of the grows of performance of high throughput screening by six magnitudes of order and diminution of its costs also by the same measure in the last ten years.

The phase in the history of biopharmaceuticals from the mid-70s to the turn of the century more and more concentrated on exploring the possibilities for exploiting the new recombinant DNA techniques. The initial enthusiasm revolved around the general vision of a very promising future, in which a new engineering capability, developing in close connection with the new science, appeared, promising the revolutionary extension of the capabilities of the homo faber to the genetic level. As various agents in the new biotechnology recall and as Pisano (2006: X) sums it up:

"The sector seemed to have little trouble convincing others (and particularly investors) of its bright prospects." (…) "Everything we knew about business and industry performance indeed suggested a very promising future for biotechnology, not just commercially but also for its ability to transform drug therapy."

There was an enthusiasm concerning the appearance of small start ups in biotechnology.

"Biotech firms were supposed to be much more efficient at pharmaceutical R&D because they were both at the cutting edge of science and unencumbered by the bureaucracy and organizational inertia of the behemoth pharmaceutical companies" (Pisano 2006: XI).

This was a concept in which only the advantages were formed into a positive vision.

Starting a new industry is, of course, a much greater and more complicated effort than providing a new basis for research, interpretation of the research's potentials for technical applications, and providing powerful technological instruments for realizing material transformations. It is also a matter of a complex of interactions on the societal side, of economy, legal regulation, organization, management, culture, and ideology and their interaction with the scientific-technological side.[13] Emerging modern biopharmaceutics found itself confronted with a whole complex of problems. Different agents had sought and found the opportunity to meet and develop jointly a path. A learning process in which a particular complex of co-operations stabilized in the early 1980s followed and set off significant changes in numerous respects during the next 20 to 25 years.

When biopharmaceutics was established, it blazed a new trail in all of the aspects mentioned. It entered a new field of experimentation with materials and organization forms where the players were challenged to learn quickly. A working form of organization, financing, and management appropriate for the specificities of modern biopharmaceutics had to be found very quickly: the solution was the integration of biotech R&D in a bioeconomy based on the neoliberalistic economic perspective, a legal regulation adapted to it, and a new specialized policy, a neoliberal biotechnology policy.

Integration of biopharmaceutical R&D into an emerging bioeconomy required first several legal steps as a basis.[14] Concerning the organization form, small start-ups were the favoured form of organization and venture capital (VC) was used for financing. If VC was utilised as financial basis, solutions for intellectual property rights, especially patenting, were also essential[15] so that the entry for venture capitalists would be secured. Putting financing on a VC–basis unavoidably required constructing an exit for the venture capitalists because they were ready for financing for not more than around three years. Possibility of going public with the VC investment onto the public equity market provided for a solution. Entrepreneurs too, as specialized managers, able to reconcile the different "logics", for example, of research and of finance appeared in the arena.

With this factors playing the most important role in the management side of the dynamics were mentioned more or less. It was somewhat contingent that start-ups stabilized first as organization forms and VC for financing. Learning from their partly contingent interactions provided for the further stabilising path in the stabilising governance within the

[13] This can be called, mutatis mutandis, a Chandlerian problem, if we take as a Chandlerian problem the development of the economic, organizational and management side able to give way to explore and exploit new technological potentials to realise new industries. (Compare Chandler 1977)

[14] I refer to two of them. The first was the possible narrowest Supreme Court decision in 1980 allowing that genetically modified bacteria can be patented. The second was passing the Orphan Drug Act in the USA in 1983 that encouraged medical breakthroughs otherwise economically unprofitable and allowed governmental interactions to further them. This act limited the working of the free market.

[15] I want to emphasize a special type of expectations and visions. They are inherent in the patents. These are knowledge claims entrenched in the practice of legal regulation, that layer where the envisioned future is set for fixing it by proprietary claims. Besides the usual written materials and visions „inscribed" in material practice as resources for expectations, systematic investigation of patenting may add a further important resource to expectation research.

frame of a neoliberalistic perspective. Within this frame, but the rise of modern biopharmaceutics was actually a prolonged path creation through a series of improvisation.

In order to make somewhat perceptible the openness of the process leading to the stabilizing outcome, the construction of the management side of modern biotechnology and the role of agency in it, I list just a few critical turning points at which ambiguous situations were decided, with marked effects on the further course. These were important steps that greatly influenced the stabilising trajectory of the biopharmaceutics.

The first point is that Big Pharma was at first rather reluctant to embark the new course. (Exceptions were Merck and Eli Lilly.) So, setting start-ups and getting financed by venture capital was not only ambition of scientists with entrepreneurial attitude and venture capitalists, but there scarcely was any other alternative, because the readiness of the Big Pharma to participate was missing at the beginning. This attitude changed by the mid-80s. From then can we speak about the returning alternative to place the new endeavour, modern biotechnology in the "visible hand", integrating it in the hierarchical structure of the firms belonging to the Big Pharma. From then we find a repeatedly returning dancing realising cooperations with small biotech firms that left them organizational place for their creativity or, much more in number, realising annexes, acquisitions by Big Pharma, beside the independent trials to realise independent biotech firms with drug production capability.

It can not be emphasized enough that start-ups and venture capital as financing form for modern biotechnology were adopted from informatics, from a field rather different from biopharmaceutics. Venture capital worked in informatics with much smaller amounts of money in comparison to the needs of the whole biotechnology innovation biotechnology innovation chain, and, for a much shorter period of time. This is in an inherent difference to the requirements of drug development. Financing biotech R&D by VC required appropriate adjustments, and led to fragmenting the financing of the value chain and creating a stock market segment. If the results of the processes listed above had been different, we can risk the assumption that the development of biopharmaceutics would also have been quite different.

A basic turn in pharmaceutics took place in recent years. Innovation in the pharmaceutical industry is not only closely strategically linked to basic biomedical sciences and biopharmaceutics, but there is a growing convergence of biotechnology and pharmaceutics. In the meantime, it seems to be a well-founded prediction that producing biopharmaceuticals is becoming the leading trend in the development of drug production.

## 5 Some consulting firms repeatedly make strong prognoses that fail

There is a widespread view that experts (scientists, advisory firms) make balanced, cautious, established visions and prognoses while "laypersons", especially from the public get repeatedly, even excessively exaggerated. This idea is partially true, but is also to challenge and ask whether at least some experts behave in the same way, and if so, when. It is to cheque how at least some advisory firms behaved in our story. I can concentrate here on only one phase of vision-making. This is the phase around the turn of the millennium. I concentrate on firms specialised on economic analysis and forecasting, such as IBM, PriceWaterhouseCoopers (PwC) and the Boston Consulting Group (BCG).

This phase is important for various reasons. The productivity crisis in pharmaceutics had already been strongly perceptible and went

through an ongoing deepening before 2000. But biopharmaceutics developed some very powerful new empirical research techniques by then; a few years before 2000 it was already foreseeable that, as an invaluable success, the Human Genome Project (HGP) would be soon finished (it was essentially finished by 2000). It presented the constituents of the map of the basic human genetic structure and were to set what all this would strategically mean concerning the original plan of a rational biotechnology. The questions also included whether the continuation of the obtained genomic breakthrough could be soon profoundly exploited for drug production. One main complementing issue was how to utilize, in a qualitatively different measure, the mighty possibilities the information- and communication (ICT) industry offered, both in data gathering and processing, in simulation ("in silico" research), in biopharmaceutical R&D.

It is important to follow the workings of globally-leading advisory firms, because they are important third party actors in making strategic assessments of economic changes: because of their influence, but also because of the tension in their status as allegedly neutral and precautious assessors, and their proud attitude of relying strongly on the opinions of a big number of scientific researchers, industrial experts and CEOs interrogated, involved this way into the process of the advice making.

Kornelia Konrad recently expressed the view that consulting firms play a decisive role in organizing expectations and apply a rich toolset of technologies of expectation-building.

"In parallel, a professionalization and commercialization of expectation-building has taken place with experts and 'promissory' organizations such as consultancies and other forecasting agencies playing a decisive role in organizing expectations in specific fields, and creating and serving a market for technological expectations by applying a rich 'toolset' of technologies of expectation-building."(Konrad 2010: 67)

My impression is, in contrast to this, that, numerous consulting firms have been using quite simplistic toolsets in making rather poor overarching forecasts as technological expectations that did not work. I shall assess two exemplars of them in the next two chapters. They essentially failed in their prognoses. They used their toolset for an inappropriate mode of approach, for forecasting the coming revolution in biotechnology and detailed its forecasted effects. The basic unsuitability of the forecasting approach, in relation to the peculiar nature of biopharmaceutics offers the basis for explanation of the failures.

The forecasting efforts in biopharmaceutics follow the standard way of forecasting. They try to identify durable and emerging trends in the environment. They try to find constellations of interactions determining (mostly probabilistically) what will happen. They look then for opportunities of accommodations and try to select that alternative that seems to be the best. At the end of this selection, advice can be formulated containing what the client has to do to best capitalize on the demonstrated opportunities.

In special cases forecasting can lead to law like formulations such as the so called Moore law in informatics. Forecasts can serve as self-realizing prophecies having a special organizing force in the dynamics of the interactions of actors.

It can be prognosticated under special conditions that crises in the dynamics of the demand side can led to a level that at least some of the agents identify unbearable, and a breakdown. To be able to prognosticate the possible solution also has special requirements. Prognostic efforts sometimes may lead to a claimed result in a happy coincidence. While menacing with a breakdown the prognosis makers may feel to be authorized to forecast those

revolutionary opportunities that can serve to prevent the forecasted breakdown, even more to enter the revolutionary growth of the capacity to satisfy new revolutionary requirements, too. It is evident that the rightfulness of such forecasts has extraordinary preconditions.

Advisory firms committed to forecasting try to close down speculations on possible futures and try to find an as deterministic script of the future in the present action space as possible. In turbulent processes such as those of biopharmaceutics are the clients put the directed questions whether there are different possibilities of capitalizing on the remaining alternatives or is at least one and is there at least some way to catch it. They treat the issues as if they were already some triggering processes or breakthroughs as facts, and take the risk of making a short-term prognosis of their full realization.

Advisory firms give a description of the issues in which consensus views with the chosen representatives of clients is included. So, another problem is that consulting firms mostly pride themselves on including the possible largest number of working scientists and industrial experts in the development of the advice, but those mostly one-sidedly prefer coming to consensus views. In this respect, the expectations the advisory firms express may work as somewhat uncritical amplifiers of the majority opinion of these players - independently of the situation that the cooperation with them aims at forecasting. They quite rarely give weighty place for individual dissenting views.

This is connected with insisting on forecasting instead of giving more place to the more flexible scenario approach. Instead of trying to uncover the action place for the players as far as possible as a multitude of alternatives from which they have to choose, they provide for deterministic guesses as extrapolations, as far as possible, and advise the players to follow the irresistible to take possible advantage from choosing among the remaining alternatives and the timely joining.

It seems, there is a tricky interaction between numerous industrial and advisory firms. Advisory firms will get some dominating role in the interaction in a stabilized cooperation with the clients if they overtake the prognosis of the direction of overarching industrial development. They acquire and make clients believe that they have more capability of overview and help to make a choice among the remaining path and speed alternatives for their concrete clients wishing "customized" advices. They have the need for steadily improving their position. Communicating their allegedly unbiased attitude, claiming doing their work as experts in the field of "the science of the future" belongs to this strive for improving their position. In this process, self-critically admitting and uncovering mistaken prognoses does not belong to the strategy.

Around 2000, there was a dominating group of exaggerated genetic researchers and industrial CEOs, concentrating on the enormous new potentials appearing in informatization and genomization of the industrial research, claiming them to be the ways to quickly come out of the depressing productivity crisis of the industry. There were players who reasoned to resist exaggeration, too. Different sorts of counter-arguments were set and in principle, more could have been found. The decisive counter-argument was then that the ontological reductionist approach is a mistaken attitude to correctly assess both the strategic role of genomics and the expectations with short run breakthroughs, not only in science but also in industry.

But there was already a rather self-referential structure of the genomics researchers' community when setting

up expectations.[16] It is an important methodological question whether advisory firms show any inclination to develop a self-referential structure when they turn to the researchers and CEOs as experts for their opinion.

In the following section, I assess two consultancies' reports. They confirm that a revolution is in the making in pharmaceutics industry as a whole. Another report bets on the informatization efforts.[17] They acquired authority in using a combination of a very rich set of partial forecasts, combining them into an overarching forecast which backs their assessment.

But there is still one more point to reflect on. When the nature of industrial revolutions is necessarily evolutionary, in the meaning of necessarily slow transition processes to qualitatively new stages, then revolutionary narratives serve for a different purpose. Nichtingale and Martin (2004) try to challenge and check the idea of a biotechnological revolution with the already available, qualitatively new evidence in 2004, and draw the conclusion that there is no real reason to speak of a biotechnological revolution in the period from the first efforts at industrial application of modern biotechnology to the early 21st century. Instead they speak of the unavoidably evolutionary dynamics of any emerging industry and dissemination of scientific knowledge. They point to the well-known historical experience and its theoretical interpretation as a historical lesson: the dissemination of breakthrough knowledge and its application in industry inevitably needs much time before the turnaround is realized.

They make the unavoidable slow evolutionary dissemination process responsible for the necessarily evolutionary characteristic of the industrial revolutions. They point to the truth of this characterization, concerning the, then around 25 years long history of biotechnology. Unfortunately, this is just a part of the whole truth. As genomics researchers recognized by 2003, genomics continued its unbelievable acceleration in finding new and new instruments, a progress that has still been continuing, but common diseases require a qualitatively different approach than rare, "orphan" diseases and this was still to start to hypothetically find and experiment with. So, it was impossible to realise a revolutionary breakthrough in solving the productivity crisis of the industry in the forecasted time period.

Revolutionary narratives may be misleading but certainly can have a role. Nichtingale and Martin (2004) draw attention to the ideological role of the revolutionary narrative: no investor would be ready to invest the needed unusually high amounts for unusually long time and in a very uncertain process, unless s/he can believe that s/he invests into something that would yield unusually significant returns within a defined time-span.

There is a special structure in the revolutionary forecasts. A normative scenario sets the requirements for a revolution on the demand side, by combining extrapolations of tendencies and knowledge whether they are still bearable at some point and there is an extrapolative forecast of the emerging processes in which revolutionary potentials offer their service. Forecasts outline the way how these alleged revolutionary potentials will

[16] A self-referential structure means that the expectation setting dynamic works in a closed arena and opens only when strongly constrained and only thereon can enter less exaggerated players the "expectation arena" for discussion. The mentioned arena needed the basic failures first to open for discussion.

[17] A PwC report forecasted and announced in 1999 automation of the pharmaceutic R&D process by 2005, brought it into connection with overcoming the productivity crisis and devoted a whole volume to it. (PwC 1999)

lead to the solution for the recognized revolutionary needs on the demand side. Provided they got persuaded from the forecasts, most important for clients in the advice is, what, probably enormous, accomplishment they will still have to make to carry out the revolution and take their share.

To repeat it: there are numerous, ontological, epistemological and pragmatic arguments that successful forecasting has very strong preconditions and so, from the rather rich set of possible dynamics, forecasting actually has a quite narrow subset to hopefully approach. Biotechnology realises a special sort of cooperation with science, as it will be outlined a bit more detailed in the last chapter. That means that there are further arguments than usual to doubt that forecasts in biotechnology can be kept as dominant approaches. In short, biotechnology explores the human body, always to expect causing the emergence of "unknown unknowns", and tries to catch profit already from unfinished research processes. These factors together may repeatedly provide for unexpected but unavoidable and, for a while, insurmountable hurdles that make certain types of forecasts useless.

## 6 "Pharma 2005: An Industrial Revolution in R&D"

The first vision, I take as an exemplar, entitled as "Pharma 2005: An Industrial Revolution in R&D", was drafted by IBM Business Consultants, in affiliation with PwC, and was published in 1998. The title is interesting itself. It speaks of an industrial revolution in pharmaceutics, assessed as a fact (!), caused by the different emerging and ongoing revolutionary changes in R&D, both on the demand and the supply side. The argumentation is roughly as follows: The report concludes on the one part correctly that, on the demand side, there is an unavoidable need to revolutionize the R&D, in the meaning of carrying out a quick breakthrough. Pharmaceutics is expanding "but evolution is generally a process of slow change and the industry now faces a challenge of absolutely unprecedented scale". (IBM 1998: 3) It is impossible for the costs of R&D to grow further, a dramatic diminution of R&D costs is to be attained, while the number and quality of new drugs has to increase. To reach this goal a "total transformation of the way in which industry performs R&D" is needed, something of a systemic change within a very short time.

> "All point to the fact that the industry must learn to create affordable new drugs, and that it will only be able to do so if it totally transforms the way in which it performs R&D."

> "One thing is certain: whatever the numbers are, 'Big Pharma' will look very different by the year 2005. It has no choice but to adopt a new strategic, tactical and operational management model consistent with the fundamental drivers of this new paradigm – and to do so fast." (ibid: 10)

In the assessment of the advisory firm, this demand requires a revolutionary change within seven years – by 2005, and this can be brought into being. What "revolutionary" means is not defined, but the context refers to expecting the rise of a new paradigm. IBM "bets" for the acceleration and whole scale realization of "industralization of R&D", a running process in that time.

The report makes a "dramatic" but optimistic vision. Not only the challenge is immense and "dramatic", there are also opportunities of the same scale. These opportunities are to be transformed into a "revolution" by clever action. The report systematically assesses some of the R&D's new chances. The possible immense increase on the number of possible targets and the development of genetic screening are taken into account. The report states that there is "a revolution in the making". The rapid multiplication of new targets by orders of magnitude is one of the

options with massive implications for revolutionizing the whole R&D process.

"There would be some 25000 new targets."

"And even if only a quarter of them prove to have genuine potential, this would still represent a 14-fold improvement on the current situation."

As the report assesses, scarcity in drug targets is only one of the bottlenecks that, allegedly, can come to an end by the new genomic possibilities in the estimated short period. The other bottleneck, that the fear of possible adverse effects of a possible new drug hinders their introduction can also be successfully overcome very soon. More than that medication will turn to prevention and individualized treatment.

"Moreover, apart from producing new targets, genetic screening will provide the means with which to identify genotypes and thus to predict who is at risk from what, together with the side effects of any medication. The focus of treatment will also expand from cure to the reversal of pathology in conditions such as epilepsy and Alzheimer's disease. So the industry's remit looks set to grow significantly. Where once it made pills and lotions, it will be increasingly involved in prediction, prevention and follow-up treatments."

The analysed expert material made a forecast that would realize in seven years. A rich set of most different trend extrapolations and their expected interactions are brought together in the report. Genomics will create new leads and new business areas; it will open markets for diagnostic testing, preventive medicines, follow-up treatments, and even support services such as lifestyle counselling. This is why all of this can be extrapolated seriously– according to the report. "By the year 2005, today's technologies will be mature". The report also presents exaggerated possibilities.

"However, the mechanisation of the early-stage discovery process could culminate in something much more radical, such as the development of drug discovery factories and 'tele-labs'. By the year 2005, the most successful pharmaceutical companies may be emulating some of the 'baby biotech' firms with research scientists, linked by powerful intranet facilities, working from home" (IBM Report 1998: 17).

Or further:

"Changes already on the horizon suggest that the preclinical stage will soon be a bridge nobody needs." (ibid.: 19).

"Emerging in silico techniques and technologies such as single cell differential gene expression and target searches in Expressed Sequence Tag libraries […] will enable the industry to identify targets with the ideal physiological and pathological characteristics. Pharmacophore technology, in silico lead optimisation, scale-up and preclinical trials will follow. Computer modelling will even provide the tools with which to perform in silico clinical trials, based on whole organ body models that test for everything, including side effect profiles and drug-drug interactions – although it is doubtful that the regulators will accept such evidence for some time. In short, within a few years, the industry will be able to move straight from the test tube to man (if not to the marketplace)." (ibid: 20)

It is evident by now that this forecasting as a whole was very much exaggerated, meanwhile some real progress was spectacular.

Because this vision of the future is based on this rich combination of extrapolations, integrated into an overarching forecast, we can rightfully ask: how much of it has been realized by 2005? Of course, it is difficult to assess such foggy prognoses that genomics "will open up the markets for diagnostic testing, preventative medicines". But it seems correct to observe that diagnostic testing for common diseases or preventive medicines on genomics base still were missed in 2005, and first of all, the revolutionary effects on R&D productivity were not realized. The error of method seems to be that only some very tentative, even when rich scenarios could have been formulated correctly, provided that serious epistemological prerequisites would have been accepted, not serious forecasts of short term revolutions transforming the working of the whole industry.

## 7 "A Revolution in R&D: How genomics and genetics are transforming the biopharmaceutical industry"

Just after the burst of the genomic bubble in 2001, The Boston Consulting Group (BCG) also published a prognosis in a volume, of which the title you find above. This is a prognosis of what will happen in biopharmaceutical and pharmaceutical R&D in the coming years. Like the IBM report the BCG report also concentrated on the radical changes that were already allegedly taking place. As BCG assesses, many had already tried to improve the development phase. In contrast, the BCG report concentrates on the research phase, and identifies promises of genomics as breakthrough possibilities for the industry.

BCG also begins by defining the challenge as a crisis. In this crisis the expectation of continuing constant double-digit yearly growth for the industry is permanently endangered. Resulting from the exclusion of any other alternative they claim that the only real way out is to increase the efficiency of the R&D process. The BCG report identifies genomics as a counterbalancing opportunity for finding the solution.

The report's message is: genomics, including genetics as the science of the distinctive genetic makeup of individuals, promises to reshaping drug R&D methods and economies radically. "Industrialised" and informatized genomic research provides more data by orders of magnitude, its processing is made already on a qualitatively higher level than earlier, and, in the end, can lead to a reduction of costs by two-thirds, and the time needed for R&D can be reduced to two years. But the process is replete with obstacles, and will first bear the costs of learning as well,

"Biopharmaceutical R&D is moving into a new era: almost every link in the value chain has the potential for tremendous boosts in efficiency or success. But these advances are not assured. Technological hurdles have yet to be overcome, particularly in the genetics wave. Moreover, because the productivity boosts are likely to be unequal and uncoordinated, the value chain itself will demand reconfiguring."…" The repercussions of genomics, in other words, are going to reach the furthest recesses of corporate constitution and culture. A true revolution, in short—and one that is already well under way." (BCG Report: 14)

As the report assures, this is already a revolution-in-the-making. But enormous hurdles are still to overcome. The BCG report makes, as a didactic example for any change it suggests, reference to a firm already benefiting from realizing the transformation it committed itself to. The mission then becomes apparent.

"It is against this background that the genomics revolution is unfolding. In their quest for improved productivity, companies should welcome the new technologies and approaches. Genomics"(…)"promises to transform how pharmaceutical research is conducted. The paradigm will shift from small-scale and serendipitous to global, industrialized, and systematic; and from methodical and compartmentalized to fluid and cross-functional. The impact on R&D economics is likely to be tremendous: in the best case, productivity could as much as double." (ibid: 59)

Made euphoric by the success of the "industrialization" of gene sequencing technology, the report paints the coming paradise onto the canvas. There is a high threshold to be crossed, but then a new world of possibilities unfolds.

"Looking beyond R&D, genomics and genetics also promise to transform the way pharmaceutical companies conduct their business in the coming years. If genetics realizes its potential, for example, treatments will become more sophisticated, markets may fragment, and the shape and value of marketing and sales organizations will change dramatically. The entire system of health care delivery, already in flux, will complete its metamorphosis." (ibid: 57)

This transformation is not merely a possibility, either, according to the report. It is already in the making, and there is no alternative to doing

likewise: those who do not will lose everything, there is nowhere to hide.

"The offer that genomics and genetics are holding out is really an offer that companies cannot refuse. Companies that fail to accept the offer adequately will find themselves not simply uncompetitive but possibly right out of contention. There is nowhere to hide, and certainly no safety in inaction. Embracing the revolution appropriately adds up to a formidable but by no means impossible task. And for companies that do it well, the rewards will be handsome. The opportunities are unprecedented. So are the challenges." (ibid.: 57).

This is a text formulating an apodictic persuasion when it speaks on the challenge, turning to the not less apodictic persuasion that the formidable future will very soon be realized, provided the needed determined commitment will be provided by the players, understanding the message.

One important element of what was actually the mission meant by "revolution" is implicitly derivable from the whole of the text in the BCG Report. It calls for determined action against the obstacles. Time is pressing, and it is impossible not to engage because this would be self-defeating. The BCG report cleverly avoids making further concrete forecasts. It only claims that there is a genomics- and genetics-revolution in the making, The process has already begun, and will continue.

Concerning the dynamics of biotechnology, the advisory firms mentioned believed to be able to recognize a revolution in the making in R&D that revolutionizes the whole industry, in a short period of time.

The BCG report is based on an extrapolation of the "industrialisation of R&D efforts" in the 90s. To assess this claim it is to see that numerous further, even more spectacular results were achieved in the first decade of the 21st century. But what is certain is that the genomics- and pharmacogenetics revolution still hasn't revolutionized the drug production even when the majority of blockbusters is already made by biotechnology.[18] Concerning the failure, it may suffice to refer to the general difficulty of prognosticating the future, perhaps refer to the inevitable slowness of diffusion even when there is an alleged revolution in the making or even a real revolution - in some part of a very complex system. But it seems even more important that the authors of the reports forgot to consider the possible role of some "unknown unknowns", in time of formulation of the reports, preventing correct forecasting. This is that the inexhaustible complexity to guess for the object of biotech research has to be repeatedly recognized through the paradox progress of research through the process of consecutive successes and failures with modelling.

One last remark: both reports address first of all those who look at the deep and ongoing productivity crisis in the industry with much anxiety, because they feel a need for a revolutionary growth in their capacity to solve the crisis. The reports simultaneously aim at tranquilizing and inspiring them by providing them with idea of the solution already unfolding as a revolution. But they also remind them on the enormous hindrances unavoidable to overcome in the process of the revolution. These clients are expected to be sensitive to the message that the radical solution

[18] Looking back onto the last decade, a summary to a new series of PwC reports, Pharma 2020, introducing the Pharma 2020 Series, states in 2011 that the golden decade of biotech has not brought a golden era in productivity of the biopharmaceutics industry. Progress has been much slower in uncovering the scientific basis than expected and the business model is not the best either. (PwC 2011: 3) The new series deals with a longer period, from 2007 to 2020, makes a detailed assessment of the changing societal and economic environment of the converging biotechnology and pharmaceutics, surveys the whole value chain, not only the R&D, but insists on forecasting what will happen by 2020 – instead of turning to foresight. A Russian proverb says: if we live to see we shall see it.

is already quickly unfolding and are reminded that they have no alternative than to follow the advice. The language of the advice has a function of reinforcing the client that s/he has to follow the message that s/he is empowered with the solution of her problems - in a prognostizable world. But all this does not really explain the setting of very courageous timing of the revolutions in the advices.

## 8 "Science is the business" – Looking for a better strategic connection between science-in-the-making and business

Forecasting can be successful even with high probability when the nature of the issue of which forecasting is made is known and the process under scrutiny is simple enough, so that trends can be seen dominating the dynamics. But do we know what sort of endeavour modern biotechnology is concerning its nature as business?

A leading economic analyst for biotechnology, Garry Pisano, says that in biotechnology "science is the business". He concentrates on explicating this and explaining what he points out, the relative lack of success in the financing, organization, and business of modern biotechnology. He analyses critically, how value is created and sustained in biotech R&D, claims to have found a structural failure and makes a "therapeutic" suggestion.[19]

Pisano (2006, 2007, 2011) forcefully argues that biopharmaceutics industry as a whole has permanently under-performed and that the basic problems in its development are that the players have not really recognized the nature of the new undertaking they have practiced. This undertaking is doing science and business simultaneously, a unification of two endeavours with different "logics". Players have not found the form of organization, of financing, business model, the management model best suited for supporting this sector's development. He argues that biotechnology has to be designed and function as a "science-based business", different from other industrial sectors that systematically make use of science.

I would like to express in a comprised form slightly differently what the "science-based business" means. It is, "business and industry built on co-producing and exploiting basic-science-in-the-making". Pisano introduced his term to refer to a new type of industry that is not simply based on systematically exploiting results of science, but on direct participation in the creation of new basic science, in scientific research itself. With this direct participation business got the very uncertain but very promising potential to realise a more dynamic and innovative co-operation with science than simply waiting for and utilising results of basic research.

> "Over the past century" (…) "science has played a critical role in a number of industries." "But it remained *outside* the boundaries of the business system. Science was a tool, an imprint, or a foundation for creating new products and services: it was not the business. From its inception biotechnology was different. In the biotechnology science *is* the business." (Pisano 2006: 1).

As Pisano emphasizes, by the modern biotechnology an innovation of innovation emerged by constructing a dynamic intersection of business and basic research as a new entity to develop.

A "science-based business" entails unique challenges, to which in history of modern biotechnology only myopic solutions have been found. He emphasizes that this is the central problem of history of modern biotechnology to explain.

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[19] "/T/he disappointing performance of the biotech sector reflects a fundamental and deep struggle between the conflicting objectives and requirements of the *science* of biotechnology and the *business* of biotechnology (Pisano 2006: 6).

His explanation is roughly as follows. When the nature of the problem is that science itself is the object of business, then three interdependent problems arise. The first is "profound and persistent uncertainty". Research in biotechnology is highly uncertain and so the success of its financing too. This means, first, finding scientific results needed to be able to develop technological products. This is connected with the question of technical feasibility. In other risky high-tech contexts, to make a comparison, uncertainty is a different problem. In these contexts it would be irrational to fear not to be able to solve the problem of technical feasibility at all. But this fear becomes rational when biotechnology is the topic. And it is to expect regularly that any reached new level of knowledge may lead to catch sight of new basic uncertainties and is unavoidable to face them.

> "And even when one finds a 'solution' it does not necessarily have clear implications for commercial R&D; rather it may instead trigger a new round of basic research." (ibid.: 9).

In my estimation, Pisano rightfully claims to have recognized a basic new type of cooperation of science and the business.[20]

Pisano speaks of Knightian uncertainty, referring to "unknown unknowns": they represent something "you did not even know you did not know." (ibid.: 8).

He takes a Chandlerian perspective in assessing biotechnology. But solving the same task, finding the appropriate organizational form for some sorts of technologies leads to result diametrically different from the story of Chandler that deals with the 19th century. Chandler identified the emergence of the "visible hand", for example the hierarchical big firms, while Pisano has got to explain how the market-based financing, some form of the "invisible hand", the VC got dominant role in construction of biotechnology. And Pisano reaches a normative conclusion: to improve the performance of the, in its history underperforming biotechnology, an innovation of innovation should be realised, the organizational side should be profoundly innovated.

Pisano does not deny the obvious that biotechnology developed and realized a working solution for its development for a while. His concern is that the industry as a whole even lost money in this phase, as he claims to have been able to identify, and the long-term sustainability and potential of this under-performing solution, due its inborn structural errors in the organization form concerning its working for biotechnology. His problem is that a solution was implemented, in which causes of under-performance were encoded from its inception but have not been recognized.

As it was already indicated, Big Pharma was first reluctant to enter emerging biotechnology and many scientific entrepreneurs, led by simplistic ideas about the difficulties to realise successful business, started start-up firms. Pisano states that the emerging new biotechnology solved the very basic business problem it had by a sort of 'tinkering', as I call it in harmony with STS terminology, in the urging situation thirty years ago, concentrating on somehow solving one sub-problem, the financing an early part of the innovation chain, from an, each other mutually influencing group of problems. With further development in financing later phases in the innovation chain this realized a working capacity for biotechnology but proves to be unsustainable, because it didn't take all of the interrelated systemic problems into account as it became unavoidable in the long run.

Pisano identifies three interconnected basic tasks in solving the fundamental problems of development of a "science-based industry" such as biotechnology. These are, first, the management of uncertainty,

[20] Besides biotechnology he names nanotechnology and new fields in energy industry as further examples.

the risk; second, the integration of the needed heterogeneous types of knowledge which the knowledge base encompasses; and third, rapid learning.

For an optimal solution, it is necessary that all three have to be taken into account simultaneously. As he assesses, the nascent industry successfully concentrated on the problem of risk, and found a solution for it. The other two strategic tasks and the interdependence of all the three were not recognised to be of equal importance.

Concerning the question of organization, small start-ups are typical for this industrial sector.[21] It is of decisive importance to see that the start-ups, expressing the essence of the biotechnological undertaking, are start-ups realising basic research in the hope of its exploitability. They are different than the usual high-tech start-ups. They make research and produce research results, first of all. With this repeatedly appearing Knightian uncertainty is essentially embodied in the working of modern biotechnology.

Further, the actors often solve their concrete practical problems without systematic reflection on the unavoidable integration of most different types of knowledge they need. This integration is somehow unavoidable in concrete practical situations and is one of the basic possibilities to raise the capacity of biopharmaceutics, when it is made appropriately. Biotech knowledge typically emerges at the intersections of multiple bodies of science, and also different sorts of practical empirical knowledge. Breakthroughs are realised from time to time, by integrating and recombining these bodies of knowledge. Pisano emphasizes that biotechnology is a par excellence innovative endeavour in the Schumpeterian understanding of innovation as recombination of the different sorts of knowledge at their intersection. (Pisano 2011: 474) Unceasing efforts in re-integration are decisive for the success.

"The power to impact drug discovery lies in how you integrate the understanding and the tools. You have to evaluate how each new tool works in relation to all the others. You have to bring all the tools and knowledge together." (Pisano 2007: 1).

This integration was not realized systematically enough in history, and development remained fragmented.

Third, in a field where essential failures belong to the nature of the undertaking because they are unforeseeable, there is a constant basic need for rapid learning; but learning is individualized in recent practice, does not appropriately occur at the industry level, there is scarcely any possibility of learning from one another's failures. Knowledge is not accumulated, because learning is essentially remaining within the walls of the innumerable small firms that exist without interaction with each other. But sharing learning, especially of the false tracks, is decisive where failures dominate in number the attempts.

"There is a multitude of small start-ups and the result is a highly fragmented industry. This leads to the problem that *every time you launch a new firm, you start the learning cycle all over again.* This is against utilising the potentials integration and cumulative learning would secure." (Pisano 2007)

[21] The problems of solving their first financial risk problems by co-operating intensively with venture capital, the unavoidable short-term perspective of some few years, the much smaller amounts than the biotech industry needs for the whole R@D were already mentioned in this article. Pisano emphasizes that the main cause of the failure is that a solution from the info-communication sector was "indiscriminately borrowed". Epistemologically speaking this means that, in biotechnology, as sufficient reasons, positive analogies had been taken into account at the beginning of the process of adopting the model given by informatics and the negative analogies as tensions to be unavoidably faced, were not taken into account appropriately or were simply abandoned or not recognized at all.

> In a highly fragmented industry "/t/here's a big opportunity lurking in one of the great inefficiencies in drug R&D, which is that most of the valuable information never gets used. When drugs fail in clinical trials – and most do – almost all the data and knowledge generated by the trials is abandoned" (…) *"/N/one of that knowledge from the failures gets shared*. Companies repeatedly make the same mistakes as their competitors in the course of the trials and aren't learning from them." (Pisano 2007, italics mine).

Pisano identifies the mechanism that leads to a continuing underperformance. His conclusion is that a new, overarching organizational, financing and management paradigm change is needed, the goal being a radical improvement of the whole management system of biotechnology, an innovation of innovation. In the view of Pisano, some mixture of cooperating big and small firms, of freeing them from the constraint of immediate profitability, looking for an appropriate mixture of cooperation of Big Pharma and VC, of hierarchy and market in the cooperation, points to the way of solution, leading to networking and knowledge-sharing efforts.[22]

This does not put an end to the defining difficulties biopharmaceutics has by its nature as science-based business but takes into account the cooperation of business and research in an appropriate way to accommodate better and better to the tension ever continuing.

In contrast to many forecasts on the future of the biopharmaceutics that try to extrapolate trends Pisano turns to understanding first the nature of the biotech, the structure of the undertaking and then, based on this knowledge, to design an appropriate mode of organization and management that is able to correctly answer the requirements of the "science-based" nature of biopharmaceutics. [23]

Whether that would allow for comprehensive reliable forecasts, to return to our basic problem with the methodologically often adventurous forecasts in biopharmaceutics, is forcefully to doubt. But it is to see that essential uncertainties reappear on new and new levels, the way of the "science-based business" is recognizing new uncertainties by stopping the old ones. Having been forced to have success by not only repeatedly exploring essential uncertainties that appear unexpectedly from the solutions reached, but even strived for such situations as source of qualitatively new knowledge, is integral to the nature of biopharmaceutics.

To come back to a central concern in this article, outlined in the fourth chapter, my claim is that the unavoidable possibility of repeated emergence of new uncertainties peculiarly limits the chances of forecasting in any science-based business. To rationalize systematic reflection on possible futures in "science-based business" including biopharmaceutics, requires a determined turn away from forecasting to the scenario method and a rethinking of the nature of advice-giving,

## 9 Conclusion

[22] In Europe state intervention is also imagined as a different type of hierarchical intervention. The growing problematic participation of hedge funding in financing biopharmaceutics R&D is still nowhere assessed as a problematic rationalization of managing the self-reproducing uncertainty in this field.

[23] It is unavoidable to consider the possibility of emergence of three types of „unknown unknowns" when problems of biopharmaceutics are to be solved. These originate in the ontological complexity of the object of biotechnology and systems biology can make progress here; the openness of the „science-based business, and the turbulent nature of biopharmaceutics' societal-economic-political environment". All of them call for turning to foresight exercise. The PwC Pharma 2020 series takes into account an earlier unnown richness of pieces of information and perspectives but insists on integrating them into an overarching forecast.

The development of pharmaceutics has led to a spiral of competition and a constantly raising need for new blockbusters. This produces a permanent tension on the demand side for uninterruptedly looking for radical visions. This was strengthened by the on-going and deepening productivity crisis in pharmaceutics from the early 1990s.

Among the different agents inclined to make radical visions, are large consulting firms. By presuming the effects of revolutionary changes in subsequent partial domains they repeatedly forecast different revolutions-in-the-making in biopharmaceutics as a whole, the solutions for the continuing productivity crisis. In the period of the turn of the century, the period under scrutiny, exaggerated assessments abounded in forecasts. Inclination to make exaggerated forecasts have been strongly promoted by the ongoing and surprising tension between the subsequent enormous developments in most different partial fields and their interactions and the continuing productivity crisis of the industry as a whole. Notwithstanding the long series of very quick and profound changes in concrete R&D and even on the meta-level, including innovation of innovation, falling short of expectations remained a regular issue. Converging pharmaceutics and biotechnology could not reinvent itself in the needed measure to catch up with the growing requirements.

The need for catching a sight of the coming radical solution as soon as possible to present it for the different sorts of payors (governments, venture capitalists, etc) and for self-confidence for themselves has given some special characteristics to the revolutionary forecasts. They speak about needs for revolution on the demand side and let simultaneously catch a sight of revolutionary potentials already available on the supply side. This is about the alleged repeated happy coincidence of needs for revolution and the allegedly simultaneously recognized revolutionary potential. Forecasts of revolutions in the output performance of the industry as a whole extrapolate effects of partial breakthroughs and, falsely, often claim to be able to indicate by when, according to them, the prognosticated revolution of the industry will be realised.

Modern biotechnology, from its inception, has developed as a new industrial entity, as "science-based business", with deep inherent uncertainty in its nature that repeatedly manifests itself by any level of progress achieved – as Pisano demonstrates. In its evolution, based on the analogy with ICT, modern biotechnology created a model of organization, of financing and of management that has been working. But this mode, one-sidedly concentrating on the „risk problem", has been continually underperforming, and is in need of a paradigm change, as Pisano correctly suggests.

It is not to doubt that partial forecasts with limited claim for their truthfulness are possible and important in biotechnology too. But more reliable partial forecasts could only be based on the changing entrenchment of the biotechnology in the larger societal-economical environment, in which repeatedly but irregularly returning new genuine surprises are to be expected, too, the deeper understanding of the nature of biopharmaceutics, the nature of a specific "science-based business". Due to this characteristic forecasting can only have an important but servant role in the needed strategic turn to hand over the leading role to the scenario methods as basic approaches to identify possible futures to contribute to action strategies that are really more robust, not only imagined to be, and are more flexible.

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