The co-evolution of institutions with the build-up of research inside pharmaceutical firms and their role in the current socio-technical industry transition

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Abstract

R&D output in the pharmaceutical industry against expenses involved has dropped dramatically. This study examines whether institutional impact may revive successful pharmaceutical research or will it permanently decline? The research question is: Under what kind of institutional conditions can pharmaceutical and biotechnology research successfully persist? The study contributes to uncovering the institutional enablers of past and future pharmaceutical innovations and constraints which retard or inhibit it.

1. Problem statement

People surviving to 70 in USA in the 1960s are now living almost to 80, well exceeding their biblical threescore and ten. Notwithstanding the general improvement in hygiene and nutrition, both medical innovations and public health spending explain most of this 10 % increase in longevity in USA (Lichtenberg, 2004). The strong positive impact of new drug launches on life expectancy in 1982 – 2001 is further documented in 54 countries around the world (Lichtenberg, 2005). These increases are robust to level of education, growth of wealth and distribution of income. Medical innovations independently contribute to increasing longevity (Schnittker and Karandinos, 2010).

The competitive edge of pharma firms fundamentally depends on their ability to continuously generate new therapeutic solutions to unmet or poorly served medical needs. To this end, the intensity of investment in R&D ranks among the highest in any industry. Alas, the R&D output of pharma industry against expenses involved has dropped dramatically. The ascendancy of research intensive pharmaceutical industry is in crisis due to steeply diminishing returns in the number of new medical innovations against almost a hundred-fold inflation-adjusted increase in R&D cost from 1950 on. The number of new drug approvals per billion dollars spent has halved roughly every 9 years (Scannell et al, 2012). The observed decline is an important issue both economically and socially. After helping to sustain the lives of men and women, has Big Pharma run its course?

2. Study objectives and research question

Observing the decline in research output raises some questions. To what extent can R&D be maintained for the benefit of patients? Under which conditions can R&D in pharmaceuticals and biotechnology, successfully and affordably, extend to new therapy fields? Do we see improved health emerging from new pharmaceuticals in the future? Do other services in health care management become relatively more important than open ward pharmacological interventions? To understand the further evolution of the R&D effort in pharmaceutical industry, we should examine the necessary external and internal conditions for businesses to pursue continuous innovation.

Previous literature on pharma innovation (especially Drews, 2000; Sewing et al., 2008; Paul et al., 2010; Gobburu, 2010; Grabowski, 2011) often focuses narrowly on technological and managerial issues neglecting the basic limitations of biological science and constraints of socio-economic institutions (e.g. Munos, 2009; Scannell et al., 2012; Hopkins et al., 2013). The literature emphasizes the need to improve innovative capacity and the support of institutions but ignores the strategic challenge of transforming systems of innovation. The systems of innovation are subject to failures in infrastructure, institutions, or capabilities (Weber and Rohracher, 2012). Time and again, forecasting the impacts of new or emerging technologies has failed. As summarized by Geels and Smit (2000) in the context of IT-technology, this arises from a number of causes. For example, new technologies are assumed to replace old ones. In fact, they generally co-exist to serve different markets and customer groups; computers have not replaced paper documents. Telecommunications have not substituted business meetings or reduced commuter traffic. A narrow functional view of new technologies presumes that e-shopping reduces physical shopping; in fact physical shopping serves other psychological and social needs such as talking with shop people or spending time with

friends beyond purchasing goods. It is easily overlooked that new technologies generate new activities; the pool of existing social needs or practices does not remain unchanged after introducing an innovation. Finally, societal embedding of new technologies creates unforeseen problems of alignment; their acceptance is retarded for reasons of convenience if many factors need aligning. Here is a gap in the literature; ground-shaking changes in the science of biology and social, ethical, and economic conditions which modify pharma industry in particular are under-examined.

My research question is: How are the external conditions in biological sciences and socioeconomic factors changing either to enable or paralyze R&D for developing cost-effective medical therapy especially for novel diseases?

In what follows I shall outline the research framework, describe study method, and elaborate the past and current co-evolutionary trends to contribute to explaining the dynamics of the current industry transition.

3. Theoretical framework

The theoretical lenses applied in this study derive from evolutionary framework (e.g. Nelson, 2008). I adapt the multi-level perspective (MLP) on socio-technical transitions developed by Geels (e.g. 2002, 2014). The central argument in MLP is that the adaption of an innovation to make a transition in human social life depends on the wider social and institutional conditions. MLP widens the unit of analysis from national (e.g. Freeman and Soete, 1997) and industry level sectorial (e.g. Malerba, 2002) innovation systems to multi-causal analyses of many layers of actors. These elements build up an innovative socio-technical system where pharmaceutical innovations as technical niches interact with the broader socio-technical regime of the health care system, which is embedded in the large scale societal landscape.

In the MLP perspective constructed by Geels (2002), the three major layers are landscape, regime, and niche levels. In the MLP model, the upper layer of *socio-technical landscape* extends over regimens on the macro-level. It includes exogenous factors to the patchwork of socio-technical regimes containing material factors such as city and transport infrastructure and macroeconomic change. The relevant actors and institutions or forces in the landscape destining changes in the pharmaco-therapeutic regime include the overall economic development, government policy, people's attitudes to health and ailment, to ethical, religious or philosophical issues, to ideals such as collective, individualistic, liberal, conservative or progressive politics, legal actors and culture, and geography. This layer is almost immune to any attempts to changes arising from regime layer in short to medium time range.

In the middle layer of *socio-technical health regime*, many actors and institutions beyond pharmaceutical firms exist and interlink. These include health service suppliers and users, such as hospital systems, providers pharmaceutical and other (e.g. surgical or psychiatric) treatment or rehabilitation, diagnostics industry, private and public research on health, training and maintaining the medical and nursing profession, and various patient and health care associations. In the subset of *pharmaco-therapeutic industry regime*, Henderson, Orsenigo and Pisano (1999) list four major

institutions of importance, namely: Public support for health related research, intellectual property protection, procedures for product approval and the structure of health care systems and reimbursement. The fifth, access to capital, is important for biotech. Their list agrees with the actors and institutions in the context of pharma and biotech of Nelson (2008). Other relevant actors include prescribing practices of physicians and the delivery system of pharmacies and other retailing outlets and wholesalers.

In the micro-level bundles of *pharma therapy niches* are embedded within socio-technical regimes. Niches are the most dynamic layer. They constitute the setup for innovations. According to Schot and Geels (2007), niches are creations of actors rather than pre-existing resource spaces. They emerge from a selection process where the environment provides direction to agents. Critical to niche construction is that they are to some extent isolated from the socio-technical regime layer, either socially, spatially or cognitively. Thus, niches are vehicles for speciation, technologically or market-wise. They may escalate and start to influence the regime layer. There is internal variation across niches. Scholars suggest that technology adaption may be slow because of the need for simultaneous appearance of multiple technologies to allow breakthroughs (e.g. Smil, 2005) and gradual since it involves the punctuated transition of a technology from one separate niche to another (e.g. Tushman and Anderson, 1986). Niches in pharmaco-therapeutics build around particular disease areas. Such nichés have specific specialists and research institutions for basic research, firm level R&D for individual therapies, and firm level marketing and production of pharmaceuticals for these niches. For example, antibiotic and cancer therapies are nichés.

This paper describes the past and current MLP structure in the pharma industry. In line with Chandler (2005), I shall describe the co-evolution of the businesses and institutions in the pharmaceutical industry ecosystem. The mechanisms of the transitions (e.g. Geels, 2004; Murmann, 2013) are the topic of a subsequent paper. Geels and other scholars have conducted several case studies in socio-technical transitions in the field of traditional technologies. Such studies include the transformation from sail to steam ships (Geels, 2002) and from horses to automobiles (Geels, 2005). Case studies of multi-regime transitions in health and life sciences include, among others, Dutch hygienic revolution of handling human excrement (Geels, 2006), introduction of psychotropic drugs (Geels, Pieters and Snelders, 2007), and Dutch health care system (de Haan and Rotmans, 2011).

Insert Figure 1 about here

Figure 1 is a tentative static display of the factors in the ecosystem of R&D-driven pharmaceutical industry. Figure 1 illustrates the nested and interacting layers of pharmaceutical research and development, adapted from Geels (2002).

Methods and data sources

My research strategy has two consecutive stages. In the first stage, following Chandler (2005) and Sabatier et al (2012), my method is historical. Using public documents and secondary sources, I construct the short narrative of pharma industry macro conditions and the co-evolving institutions to support its R&D activities. In the second stage, I shall conduct interviews of relevant actors from

the institutions identified in stage one to elaborate the steps of co-evolution. The informants are international experts (n = 100) in the fields of basic and clinical research, government officers and pharma executives in four countries: Finland, Germany, United Kingdom and United States. Based on historical data and current interviews I construct the framework of the socio-technical system whose dynamics I shall further study. This paper reports the historical background and the pilot interviews of 19 Finnish informants.

4. Past co-evolution of pharmaceutical industry and institutions

Industries emerge and grow if and only if conditions of the external environment and the internal setup of firms and their capabilities coincide for fit in time and place, constituting a dynamic co-evolving ecosystem (e.g. Malerba, 2002; Geels, 2004; Murmann, 2013). For the ascendancy of pharma industry from after World War II until yesterday, significant external opportunities for utilizing and further developing its capabilities were provided. I have used the works of Chandler (2005), Temin (1979), Liebenau (1985, 2013), Lee (2003), Achilladelis (1993), Henderson, Orsenigo, and Pisano (1999), and Galambos and Sturchio (1998) as general sources on the history of pharma industry focusing on Germany, UK and USA.

Evolution of the pharmaceutical industry

Traditional pharma firms in Germany such as Merck and Schering arose from local pharmacies preparing alkaloids and other then known medicines. The large scale pharmaceutical industry emerged after 1870 from applying the skills in organic chemistry of dye manufacturing firms such as Bayer and Hoechst after it was realized that dyes used to stain bacteria often killed them but did not harm mice or men. New vaccines were found in academic research and manufactured by those firms. Somewhat later in USA, the growth of production in firms such as Wyeth and Pfizer was based on US public health system demand on sera and antitoxins, originally developed in Germany. In UK, major pharma firms such as Allen & Hanbury's and May& Baker were importers and wholesalers of medical materials arriving from colonies. Thus, early national pharmaco-therapeutic systems were different.

Firms in Germany and USA also extracted and purified substances, such as hormones, from natural sources. In USA, another technology path not dependent on synthetic chemistry was to search for new antibiotics from soil and isolate and manufacture them by biological methods such as fermentation. The actual trigger to large scale drug manufacturing in USA and less in UK were government orders for penicillin during World War II. US firms had superior capabilities to apply fermentation method to this end.

Research and development

Research laboratories emerged at pharma and dye firms in Germany by the end of 19th century. Their goals were to purify or synthetize natural products, create new dyes and improve their manufacturing processes. The prevailing chemical paradigm of drug action was visualized by Ehrlich: ligands act on receptors like "key in the lock" (Drews, 2000). New molecules, such as

sedatives (barbiturates), antipyretics and analgesics (Aspirin®) were put into market. Although these products relieved symptoms, almost no drug really cured the patient. Among the major goals was to effectively treat tuberculosis and syphilis.

Before 1940, pharma spending on R&D was higher in Germany than in UK and USA, where repackaging and advertising of brands was important. The research cascade of discovering new molecules from dyes produced sulfa antibiotics. From this chemical family of sulfa compounds, researchers incidentally developed diuretics, the first antihypertensive drugs, and also the first oral anti-diabetic drugs. Contrary to short term application of antibiotics, treating hypertension and diabetes was long term therapy. This development further pushed R&D in firms on studying solutions to chronic diseases (e.g. Daemmrich, 2009).

In those days firms only had the skills to study small ligands and resources to modest therapeutic trials with undisputed endpoints. Adverse events, although sometimes severe, were usually diminished when a variation of new molecules structurally close to the pioneering ones were introduced. As it turned out, due to fortuitous biological facts, many prevalent diseases satisfactorily yielded to treatment with small molecules.

Firms and investors finally realized the importance of spending more funds on in-company R&D in pharma for exceptional returns. The impact of R&D on business performance both enabled and justified this. In Germany, R&D investment arose over 10 % in the 1960s (Dominguez-Lacasa, 2006). In USA, the level of innovation expenditure rose from 4 % of sales in 1951 to 8 % in 1960 and 10 % in 1970 (Temin, 1979), and to about 20 % from 1980s until present.

Co-operation with academia and public research

Systematic co-operation between industry and academia started in Germany around 1900. Much of early research was conducted with professors in top universities (e.g. Burhop, 2009). University ties were later developed also in USA where local contacts had been more important earlier (e.g. Furman and MacGarvie, 2009). The large-scale manufacture of penicillin in USA and UK was a major co-operative venture between universities, government and firms (e.g. Kingston, 2000).

The nature of relations between top professors and industry was earlier more personal than institutional. The co-operation gave pharma firms access to publicly funded health data. The impact of public research on product development in pharmaceutical firms is estimated to be substantial (e.g. Cockburn and Henderson, 2000). Downstream industry is closely linked with upstream academic institutions, and knowledge flows both ways. The exchange was reciprocal, since many industrial scientists also took academic positions. Public sector science created huge science workforce also available for industry.

Patents

But for the episode in 1791 – 1844 in France, patents to pharmaceutical products emerged late in the history of the industry. Unlike chemicals, medical products were not patentable until in 1948 in UK and in USA (e.g. Kingston, 2000; Gaudillière, 2008ab). Process patents were issued in Germany since 1877 but substance patents were introduced in 1967. Early antibiotics, such as

penicillin and sulfa were not patented. This is also the case with vaccines, which were based on public research but manufactured in firms with biological methods. Since the 1950s, proprietary patents became industry standard.

The issue of drug patents has always been controversial due to the crossing interests of public good and private gain. In terms of R&D efficacy, whether the temporary manufacturing monopoly granted by patents retard or boost innovation remains debated. German dye firms rose to world leadership and remained there under no full domestic patent protection but due to their superior size and understanding of organic chemistry enabling to work around any competitor (Murmann, 2013).

Drug regulation and prescribing

The regulatory legislation on pharmaceuticals developed slowly and was accident-driven (e.g. Rägo and Santoso, 2008). Drug regulation builds on three criteria: quality, safety and efficacy. The basic requirement for good quality emerged from the established tradition of pharmacopoeia containing specifications for the purity of preparations obtained from plants. After the diethylene glycol poisonings used as solvent in a sulfa elixir in 1938 FDA required proof of safety for approving drugs. After the thalidomide catastrophe in 1957 causing deformations in thousands of newborns the governments in Europe and USA made pharmaceutical product approval mandatory and codified guidelines required for selling products. The practice of regulatory approval was established in Europe by mid 1960s (e.g. 1960 in Germany, 1964 in Finland and 1965 in EEC). However, detailed regulatory guidelines for product approval and monitoring adverse event were established first some years afterwards (e.g. proof of efficacy in 1962 in USA, 1972 in Finland, 1976 in Germany). Later, regulatory requirements were to include novel aspects, like documenting added medical and economic benefits and post-launch surveillance programs.

The tradition of prescribing drugs by physicians also emerged over time. Prescribing narcotics only by physicians became mandatory in USA in 1904. Non-narcotic drugs could be purchased without prescription until 1938 in USA, and this FDA guideline became a law first in 1951. Prescribing sera and vaccines was restricted to physicians from 1895 on in Germany.

Pricing and reimbursement from insurance

The effects on mortality of antibiotics were spectacular even without the evidence from large clinical trials. The pricing of their life-saving benefit soon became an issue. Providing health care to everybody in need but unable to afford the prices was a huge social concern. In the post-war economic boom, the idea of welfare state gained acceptance. The economic development in Europe and USA went on almost undisturbed for 30 years until 1970s. This growth created the base for health care funding and reimbursement of drugs by increasing taxation in Europe (e.g. Piketty, 2014). In USA, private insurance covered the majority of employees. As the political pressure for equal opportunity to curative therapies regardless of wealth grew higher, many European countries introduced social security reimbursement schemes to the emerging life-savers after the NHS was introduced in United Kingdom in 1945. By 1970's most EEC countries had set up an insurance system to meet some if not all medication cost of the suffering but penniless (1972 in Finland, 1976 in Germany).This included the collective sharing of medication cost with insurance policies so that most patients could afford the new pharmaceuticals becoming available.

Pharma industry business model

Long term medication provided a lucrative earning opportunity for the industry. Consequently, new therapeutic segments addressing disorders in therapeutic nichés such as neurology, asthma, cancer, and the cardiovascular and gastrointestinal system were continuously launched year after year.

One consequence of mandatory prescribing was that payers – consumers and insurers - were separated from expert physicians who decided on therapy but did not face the economic consequences of these choices. This shift in regulation created a new emphasis on marketing products to doctors rather than to consumers or pharmacists. In marketing, German firms used sales representatives to doctors in the 1930s (Thoms, 2013) whereas in USA firms still advertised directly to consumers. The extensive marketing toolkit was adapted in the industry by 1950s.

According to Temin (1979), patents and mandatory prescriptions created price inelasticity and encouraged own manufacturing and marketing rather than R&D out-licensing. Although products could be patented, the R&D methodology of the industry could not. Hence, no center of industry arose. The big pharma remained fragmented and became vertically integrated, delivering both profit from sales and return to equity at the level of 20 % until 1990s.

5. Current and emerging institutional constraints

Current statistical data show that FDA new drug approval rate in 2000 - 2009 is at its 25-years low (Kaitin and DiMasi, 2011). This recent collapse is aggravating the crisis of pharma R&D productivity. How have the institutions changed by today and how do they evolve in the future?

Research paradigm and biotechnology

Biologic realities in diagnosing and treating diseases have changed dramatically since the early triumphs of the industry. Many of the large illnesses already have appropriate and cost-effective therapies. Consequently, the number and magnitude of new opportunities has shrunk very much. New pharmacological therapies for still unmet medical needs must either be of paramount value in saving lives or reduce the hazards and costs of current therapies. The emergence of biotechnology occurred early within pharma industry in the fermentation process of making antibiotics, manufacturing of vaccines and other antibodies, and assays for standardizing hormones from animal sources. After most big players in the pharma industry turned to the chemical paradigm of screening small molecules for new products, small biotechnology startups of university researchers were born, using the biological methods such as fermentation now in decline in big firms (Daemmrich, 2009).

Recombinant DNA gene technology was first utilized in the manufacturing of insulin, growth hormone, clotting factors and other such biological medicines. The capabilities in this field were very different from drug design by screening and organic synthesis which was the base for creating new small molecules. Drug design by epigenetic research required skills closer to biology than chemistry. New biotechnology flourished in USA much earlier than in Europe (e.g. Lehrer, 2007).

However, despite the huge enthusiasm in personalized gene-based diagnosis and therapy relying on increasing stratification of large diseases in subtypes, little progress has been made (e.g. Hopkins, Crane, Nightingale and Baden-Fuller, 2013). The diseases still in need of effective medication often have much higher pleiotropy, that is, the simple ligand-receptor model is replaced by many-on-many relation between ligand and receptors. At the same time, new treatments may necessitate either poly-pharmacy or larger molecules. Adverse events would be more numerous due to both the large size of the therapeutic molecules and the multi-faceted nature of the morbidity. Modified RNA molecules for gene silencing cannot be transported to cells (e.g. Daka and Peer, 2012).

Although biotechnology has delivered few new therapies, it is increasingly used in manufacturing processes, for example to make the new cholesterol-lowering drugs known as statins. It is likely that the benefits of biotechnology will be realized mainly in diagnostics, biomaterials and agricultural business (e.g. Gaudillière, 2009).

Informants on R&D

I have condensed the results of the pilot phase interviews on future health research to four major findings which the majority of the informants reported alike. First, defective understanding of many basic biological processes constitutes a bottleneck for progress in providing therapeutic solutions for maladies with unmet or only partially satisfied need. Although historical evidence shows that therapeutic advances have been made on empirical basis without understanding the mechanisms involved, the advances in genomics and diagnostics are not easily translated to therapeutic benefits without much more solid understanding of basic functional and molecular biology and their systemic effects and interactions due to pleiotropy. This is more important for problems in neurobiology and other disturbances in homeostasis than for infections and cancer.

Second, because progress in basic and clinical science is more likely in the treatment of cancer, the industry now focuses much of its development on oncology. New antibiotics are not the most preferred target for product development, since they are short term therapies. Perceptions on progress in neurophysiology are mixed, since the basic biology is highly interconnected and the relations between biology and psyche are immensely difficult to grasp (e.g. Bain, 2006). Hence, treatment is more likely to address epiphenomena rather than deep causal connections.

Third, but for cancer, no significant practical advances in the following ten to fifteen years are likely in genomics, personalized medicine or stratification of large diseases to subgroups responding to specific therapies. This is because pleiotropic effects will interfere and much work is needed in basic research to understand them, as already pointed out above.

Fourth, the funding of basic biology research competes with research on biomaterials, nanotechnology and diagnostics, or on prevention, and intensive or terminal care. Allocating resources for preventive interventions rather than basic and pharmaceutical research is a likely health policy choice, although this varies from country to country. As a result, new insights in basic biology may easily get postponed when the trend on funding focuses on practical healthcare issues.

Co-operation with academia and public research

Like the discovery and manufacturing of antibiotics in the 1940s, research on mass production of biomaterials in USA in the 1960s benefited enormously from public funding. However, industrialists were skeptical towards co-operation with large public institutes since the discoveries were not patentable (Yi, 2009). Instead, industry chose to work with small start-ups. Universities thus became directly involved in entrepreneurial activity as institution rather than supplying technical expertise through personal relations. There is an increased perception of universities as venture incubators.

Translational medicine is dedicated to delivering new clinical therapies from basic research. For increased efficacy, more cooperation with academia, industry and health care is needed (Bornstein and Licinio, 2011). The obstacles are many, but one relates to advancing academic careers. University tenure and industry research cultivate different types of activities and publications, which is currently worsened by the "publish or perish" cult.

Regulatory

Concerns on the effect of regulation on innovation were expressed long time ago (e.g. Grabowski, 1982). During the past decades, the amount of data on any new or old molecule has exploded. The sheer mass of information has added on the requirements for efficacy and safety data. Although harmonization processes to unify regulatory procedures within EU, and across EU, USA and Japan are ongoing, one universal approval process has not been reached. New gene and nano technologies and combining diagnosis and therapy create new challenges. Patient compliance, pharmaco-economics and degradable biomaterials add wholly new dimensions to regulatory assessment.

Even if some drugs for restricted use in rare diseases get fast approval, their total reduction of the regulatory burden is small. Until recently, regulating generic products was relatively easy, but this will be more complex in the realm of biological medicines. The pharma R&D policy in USA has focused on big indications due to increases in FDA requirements since 1962 (Schnee, 1979). This is likely to lead to innovation exhaustion more easily than if the search for new chemical entities were spread over numerous nichés.

Prescribing, pricing and reimbursement

For a number of years, health care costs have grown more than GNP. In Germany, the inflation adjusted mean drug reimbursement cost per capita rose over 200 % between 1980 and 2000, amounting to 500 € already ten years ago (e.g. Mossialos and Oliver, 2005). In USA, private health insurers carry even higher levels of cost burden (e.g. Scherer, 1993). The ways to control this increase in Europe now include a mix of many means, varying from country to country, such as increasing co-payment and no reimbursement for over-the-counter (OTC) products on the patient side. Providers are controlled with diminishing levels of reimbursement, applying price ceilings, monitoring doctors' prescriptions with budgets and incentives, promoting generic substitution at pharmacies, and releasing older prescription drugs to OTC.

When new pharmaceutical therapies are replacing old ones their prices are regulated in Europe. Price discussions focus on add-on benefits that new pharmacological entities might offer. More and more emphasis is put on the evidence-based approach over the clinical experience of individual physicians. Inside EU, prices are supposed to be harmonized, but in fact the price of the same preparation differs from one country to another. Differences in pricing enabling parallel import are obstacles for setting up pan-European social security system for reimbursing health care irrespective of nationality and state of residence. Personalized medicine brings problems in combining the pricing of a therapy kit containing both diagnostics and medication (e.g. Leopold et al, 2013). In USA, prices are not regulated beyond reimbursement ceilings given by insurers, although Obamacare might change this.

Within a nation's health care system, pharmacotherapy competes with intensive care for the seriously ill and with preventive non-medical interventions for funding. These policy choices are national. Today, the social insurance based drug reimbursement system is congested with ever-increasing demand on subtler services with higher prices of medication for smaller patient groups at times of less economic growth and higher national debt. From the manufacturer's point of view, fixed costs of developing a product for less prevalent yet grave diseases or in personalized medicine are insensitive to therapy segment size. Innovating therapies for smaller disease segments is likely to be relatively more expensive, which creates an urge to push prices ever higher.

New attitudes emerge

In a study on the introduction of consequent niches of psychotropic drugs, Geels et al. (2007) point out that cultural issues influence the ideas of health, therapy and healing in long waves. These mechanisms are also manifest in the changing identity of health care system. As observed by de Haan and Rotmans (2011), the Dutch health care system may be moving away from the cure-centered regime characterized by centralized, collective, specialized hi-tech authority of physicians having faith in science. Health is here defined as the absence of disease. Contrast this with the idea of health as well-being. The health system co-evolved with increasing public financing, but it faces a lot of stress now. Some sort of integrated well-being and system care might emerge in the future.

The anticipation of innovative "miracle" health technologies may, however, reinforce the techno-medical approach. According to Webster (2002), people are categorized as ill according to a biomedical model, not whether they are feeling bad or have symptoms. This deconstructs the physical body as the locus of health and illness. As a consequence, the doctor patient relationship turns to rely more on technical knowledge than trust. However, the increasing diagnostic power of new technologies does not offer physicians new abilities to influence a patient's prognosis.

The relations between science and technology have changed since the 1980s. Previously, science dominated technology whereas now technology is more and more conflating to science and suppressing it (Forman, 2008; Gaudillière, 2009). This change in the general mindset is likely to neglect the funding of basic research and focus on developing quick solutions. Favoring "techno" medicine is at cross-purpose with the difficulty of basic scientific advances.

Another twist in changing or manipulating attitudes is the medicalization of disease meaning that any disease should be treated pharmacologically so that the pharmaco-therapeutic regime would

coincide with the health care regime (Williams, Martin and Gabe, 2011). This could occur if industry influences both physicians and patients to this end.

Finally, people's willingness to collective social responsibility of health care has eroded. Taxpayers are less interested in co-financing the medication of their poor fellow citizens. They also point out that low cost intervention measures to adopt healthier lifestyles are available, yet neglected. Individualistic consumers and relentless lawyers litigate on drug side effects. The reputation of pharma industry has declined in the past decades.

Pharma industry business model and financial sector

Traditional pharma industry has reacted to the emergence of biotechnology entrants in two ways. Firms have either established joint venture partnerships with biotechnology providers or started building internal capabilities for entering the field (e.g. Galambos and Sturchio, 1998). Networks between traditional pharmaceutical industry and biotechnology startups are dense (e.g. Roijakkers and Hagedoorn, 2006). After some initial successful products of biotechnology-based R&D in the 1980s (Chandler, 2005), no biotechnology revolution is ongoing (Hopkins et al, 2007). Instead, the pattern observed is that of incremental innovation rather than disruptive technological change.

The measurements of Rafols et al (2012) suggest that both the total number of scientific output in publications from R&D laboratories of pharma industry declines and that the number of their external collaborators as authors ascends. This pattern suggests increased outsourcing and shrinking knowledge production in own pharma R&D in 1995 - 2009.

Current financing model of US bio-pharmaceutical firms allocates less for R&D and more for stock paybacks and dividends (Anderson et al, 2010; Lazonick and Tulum, 2011; Gleadle et al, 2013). In fact, the changing expectation of the stock market on payback times retards and constrains the ability to generate new drug candidates to pharmaceutical firms since its investment-selection processes are inefficient (Hopkins et al, 2013). As planning horizon for venture capital is not much more than three years, Pisano (2010) asks how sustainable is the vertical disintegration of R&D and manufacturing in pharma?

Insert Table 1 about here

The economic growth in 2010s is likely to be much slower than in 1950s to 1970s (e.g. Piketty, 2014). Although pharma industry has become truly global, pricing constraints and ever increasing development costs are likely to lead to further significant decreases in margins. The observed changes in the multiple-layer socio-technical system derived from literature and informants between c.a. 1950 and 2010 are summarized in Table 1.

6. Discussion

Institutions in the regime level co-evolved at times when pharma industry developed its R&D capabilities. This division of labor resulted to most of new product development carried out in firms whereas academic research institutes provided the industry with considerable data on their findings in basic research. Basic and industry research developed symbiotically with exchange of people and ideas. Patent legislation enabled firms to protect R&D findings. Governments were providing opportunities for the industry to expand to large scale biological manufacturing, which later helped the firms to build new capabilities in R&D. Drug payment schemes and mandatory prescriptions created huge markets for major long-tern therapies. Regulatory authorities approved and monitored drugs, which increased the legitimacy of the industry. The pharmaco-therapeutic regime developed from fairly independent, even autonomy-seeking actors (industry, regulatory, academy) toward an ecosystem with deep reciprocal interdependencies.

Proposed reasons for decline in R&D

The productivity crisis and decline in pharma R&D output has provoked various explanations on niche level. Pammolli, Magazzini and Riccaboni (2010) show that R&D investment since 1990 is increasingly shifting to new higher risk areas, characterized by huge unmet therapeutic need (e.g. central nervous system), but unknown biological mechanisms. There seems to be no gap in productivity between US and European firms. Attrition in the clinical phase II and III trials remains the most important determinant of overall R&D efficacy (Paul et al, 2010).

Until recently, solutions to find enough suitable lead targets for pharmaceutical innovations were looked from mechanizing high throughput in vitro and in silico search in drug discovery space (e.g. Drews, 2000; Nightingale, 2000) or increasing variation in organic synthesis (Schreiber, 2000). Like in mature industries (e.g. Utterback and Abernathy, 1975), R&D process improvement has received considerable attention (Sewing et al, 2008; Gobburu, 2010). The widening use of biomarkers in diagnoses and the role of genomics in personalized medicine put forth the importance of developing diagnostic methods to co-evolve with more individual treatment (e.g. Amir-Aslani and Mangematin, 2010). Many eminent scholars are optimistic about applying genomics in innovative drug therapy for high unmet need such as Alzheimer's disease, cancer and autoimmune disorders (e.g. Grabowski, 2011).

Munos (2009) argues that the decline of R&D productivity is not necessarily a sign of failing R&D, since the rate of new drugs appearing is still quite constant annually, but the research paradigm needs revision. The emerging paradigm in sight rejects the pursuit of maximally selective ligands dating back to Ehrlich and starts searching drugs which target multiple proteins, creating network pharmacology (Hopkins, 2008). Indeed, many complex traits or diseases, such as obesity or metabolic syndrome, seem to arise from emerging perturbations of selected loci in large molecular networks (Chen et al, 2008).

Moreover, there is abundant evidence that both drugs (ligands) and proteins located in cell membranes are highly promiscuous in their binding affinities (Kell et al, 2013). In addition, there is no one-to-one correspondence with the genome and phenotype or disease. Instead, there is abundant pleiotropy – many-to-many correspondences of genotype and phenotype – in diseases such as

metabolic syndrome, cancer and immune-mediated phenotypes, although there is no consensus of the amount of pleiotropy in humans (Sivakumaran, 2011). The new research paradigm definitely challenges the reductionist “techno” assumptions in current medicine and pharmacogenomics. Alas, progressive innovation in pharmaceutical therapy may also become far more difficult.

As reminded by Nelson, Buterbaugh, Perl and Gelijns (2011), the pattern of innovation in the medical field across diseases is also very uneven. For example, many discoveries in cancer therapy were made by experimentation and not by fundamental advances in basic science. On the contrary, scientific progress in genomics on cystic fibroids has not resolved the problem how to treat them pharmacologically. Medical know-how progresses with multiple pathways; diagnosing and learning in clinical practice aside from technology and basic science.

Studies indicate that large therapy market segments (Acemoglu and Linn, 2004) and economics of scale in R&D experimentation (Nightingale, 2000) foster pharmaceutical innovation. However, mergers in big pharma correlate negatively with performance and innovation (Ornaghi, 2009). Mergers have resulted in declining R&D output, assumedly because the concentration of decision making has led to closing parallel research pathways. This has reduced variation which is needed to cope with inherent uncertainty in R&D (Comanor and Scherer, 2013).

Some social scientists regard the narrow approach of taking just niche level technological issues into consideration as unjustified, even dangerous. On regime and landscape levels, individual differences in responses to the personalized therapies deriving from pharmacogenomics raises fundamental ethical and economic issues in the current pattern of pharmaceutical therapy and its institutional frame (Deverka, Vernon and McLeod, 2010). The biological fact of huge variation in response to extremely expensive drugs brings about difficult societal questions. For example, Fleck (2012) asks which individuals should we treat and pay the therapy collectively. A pharmaco-economic solution by taking disease specific characters into account on defining price ceilings, as suggested by Camejo, McGrath and Herings (2011), does not resolve the ethical question.

Due to great inter-individual variability, the idea of personalized medicine is inherent in every physician’s therapeutic endeavor; today medicine is more like art than science as always, notwithstanding genomics (Tutton, 2012). The idea of predictive and preventive medicine available without a doctor’s mediation neglects bedside judgment and takes away physicians’ responsibility. It also undermines the solidarity of the social insurance ideal of the welfare state giving everybody the means for medication (Rose, 2013).

I suggest that there is still one plausible reason for diminished R&D productivity on niche and regime level, which can be distilled from the above findings. The industry, intentionally or not, took measures to decrease the variation of possible drug candidates for R&D. This happened by focusing R&D on major indications, neglecting spillovers of search programs, pursuing to promote only patentable products, and expressing time to time hostility against joint government-sponsored research initiatives. Moreover, mergers tend to narrow R&D portfolios, whereas increased research of diagnostics and process innovations take away funding from therapeutic research. Finally, controlling external biotech venturing is less effective that supervising in-house research. In systematically reducing variation, the industry neglected the fundamental uncertainty of the

innovation process at its own peril. These measures eroded the capability base in R&D. Recent reversal to enter risky fields occurs too late relative to cost level.

Alternative futures

For Chandler (2005), the success of pharmaceuticals resembles other global industries (Chandler, 1990). It was rooted in building capabilities in R&D and manufacturing, and reinvesting in R&D to create barriers to entry, in defining strategic boundaries and not entering unrelated diversification, thus recognizing scope and limits to growth, and in real life experience of managers. Skilful and timely utilizing of these enormous opportunities was essential. Individuals and firms made managerial innovations to acquire the means such as financial and entrepreneurial knowledge, resources and capabilities to organize conditions for satisfying huge unmet needs in a very large scale. Chandler's historical analysis is supported by quantitative analyses of the sporadic development and heterogeneity of the pharmaceutical industry (e.g. Bottazzi et al, 2001, Malerba and Orsenigo, 2002). To what extent is Chandler's epic view accurate in the 21st century at regime level when pharma industry disintegrates vertically to abandon R&D?

Langlois (2003) considers that redistributing risk to buffer uncertainty inside a firm is an important driver in vertical disintegration, which started happening just after the times Chandler was describing. This idea, at first hand, seems plausible for the pharma industry utilizing external R&D capabilities from biotech. However, the risk of R&D in itself does not go away; one should look at the system of biotech R&D plus pharma firms. In the end, pharma giants are not better off by outsourcing R&D if they do not receive a pipeline. As Pisano (2010) explains, venture capitalists would not wait for 10 years and invest one billion € for one new product. For lack of cash flow from current business, no biotech "science" firm could do this. Rather, biotech ventures want to be liquid soon to buffer for their uncertainty. How to manage and reward long-term risk in public or private pharmaceutical R&D remains open.

According to O'Sullivan (2010), Chandler assigned minor and transitory importance to the financing of big business. For Chandler, the financial market was important only for areas with high fixed costs, such as railway construction. He conjectured that over-financing occurred which led to overcapacity, increasing power of investors in boards, unfamiliar with specific businesses, and opportunities for mergers by tycoons. One wonders if this also applies for biotech R&D plus pharma. As Lazonick (2010) quoting Chandler (1990) makes clear, organizational capabilities painstakingly created and maintained rather than outside finance were needed to cope with changing technologies and market opportunities. Profits were reinvested and the basic goal of industrial enterprises became long-term profits based on long term growth.

Although Lazonick suspects that some results of Chandler are not valid in the 21st century, his method is. Lazonick emphasizes the social conditions for innovative firms: Strategic control, organizational integration and financial commitment. All these three elements are missing in the econometric biotech R&D plus pharma business model and the capability base remains underdeveloped in both of the two component organizations. Importantly, optimizing firms are *not* innovative firms. The optimizing paradigm of standard economic theory does not hold for research investment in pharma. Moreover, the processes of industry and institutional evolution are not

intentional, as actors and institutions emerge and change in an un-concerted manner to change the future (Bergek et al, 2008). Examining the processes of selection among institutions suggest that agents are unlikely to anticipate the results, these processes are path-dependent and non-ergodic (Brousseau, et al 2011), not “optimal” in any sense (Schot and Geels, 2007).

Recently, scholars have provided new evidence that biotechnologies have reached a stage of technological saturation, precipitating an innovation cliff (e.g. Fernald, Weenen, Sibley and Claassen, 2013). These results are in line with observed sequences of succession in science (Taylor and Taylor, 2012), lifecycle models (e.g. Utterback and Abernathy, 1975) and the evolutionary dynamics of the “punctuated equilibrium” pattern (Tushman and Anderson, 1986).

If an innovation cliff is likely and less and less venture capital is available for biotech or pharma R&D, then I suggest that the only way institutions on regime level can revitalize research is to increase variation by huge public investment, which also Freeman (2004) thinks is crucial. Otherwise, as patents run out, the return to pharma industry’s pre-war business models of generic manufacturing and retailing with little R&D seems quite likely. However, getting public funding may be hard in the future, since one has to compete more fiercely with declining track record in the larger health care regime outside pharma industry regime. Improving the compliance of existing therapies and launching preventive interventions at population level are gaining wider acceptance.

7. Contribution

The study proposes three reasons for the decline in pharma R&D. First, industry’s own actions restricted variation in R&D candidates. Second, basic biology became more difficult. Third, institutions supported pharma R&D less. I formulate two hypotheses to be tested: (1) at niche level, innovation cliff in pharma research steepens due to slow progress in basic biology, (2) at regime level, public funding to compensate the decreased interest of pharma firms and venture capitalists to invest in basic biology diminishes due to changes in landscape: economics, attitudes, culture and values. Put together, pharma R&D goes into a tailspin. Big pharma exits innovative growth phase and enters mature phase like chemical and petrochemical industries did years ago.

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Figure 1 Three layers in pharma industry socio-technical system

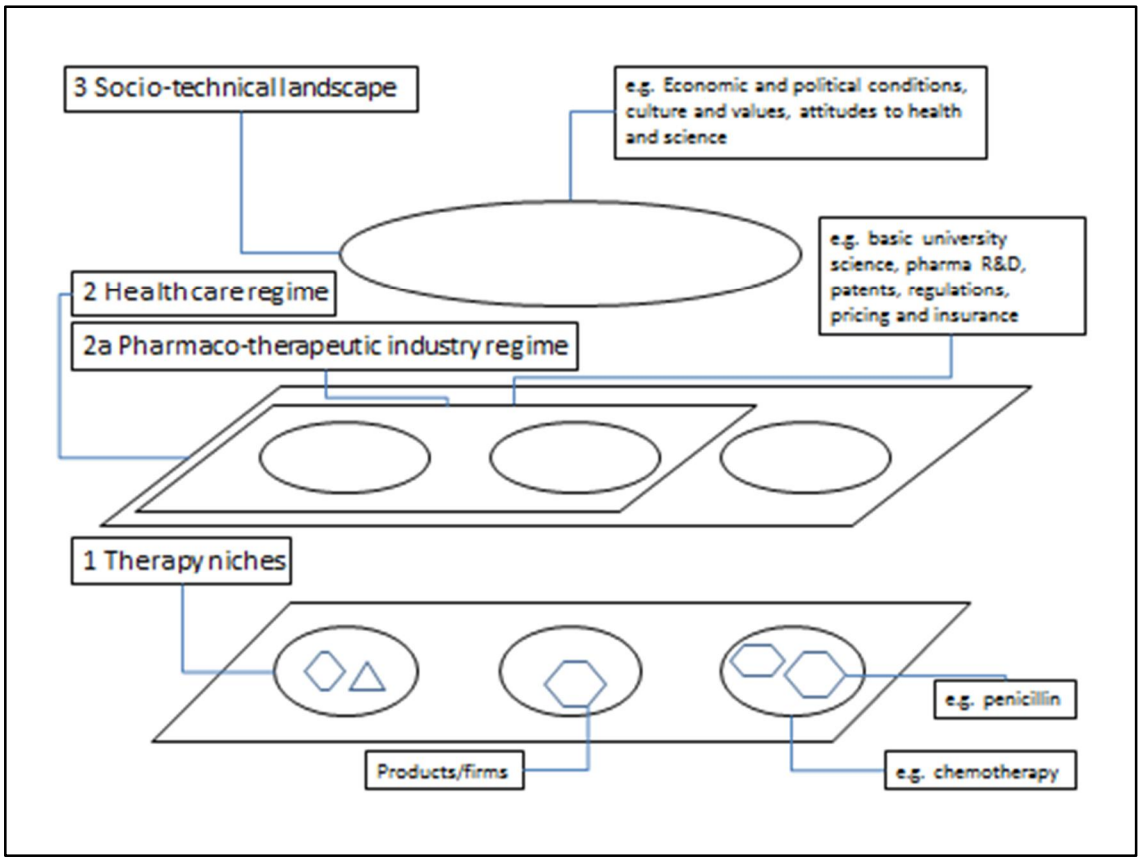

Table 1 Effect of changes in the multi-layer socio-technical system of Big Pharma

Year	1950	2010
1 Therapy niches		
Therapy segment size	Large	Small or increasingly stratified by diagnostic means
Research focus	New molecular entity	Process/production
Pleiotropy and system effects	Low	High
Unmet needs Therapeutic segments	Major diseases, immense opportunities	Rare diseases, few opportunities
R&D cost	Affordable	Not affordable
Product development	Low cost short lead time	High cost long lead time
Big Pharma business model	Vertically integrated R&D	Outsourcing R&D
Bio-pharma innovations	Manufacturing process	Manufacturing process, diagnostics, biomaterials
Generics and OTC	Diminishing	Increasing
2 Health care regime		
R&D actors	Universities and other public research institutes	Venturing firms of universities and research institutes
Research paradigm	Ligands and receptors	Biology and epigenetics
Universities	More co-operation	More competition
Physicians	Trust and prognosis	Data and disease technology
Regulatory authorities	Shorter list of requirements	Higher number of patients
Pricing	Benchmarked relative to other therapies	Absolute price ceilings, health economics
Insurance firms or government	Partly or fully reimbursed	Increasing restrictions on reimbursement
Diagnostics	Separate from therapy	Connected with therapy
Patents	Increasing effect to protect innovations from generics	Diminishing effect due to short duration
Health politics	Pharmaceuticals and vaccines	Prevention and terminal care
Investors	Attracted by high earnings	Skeptical of industry future
Venture capital	Absent	Controls R&D investment
3 Socio-technical landscape		
Attitudes to basic research	Primacy of science	Primacy of technology
Attitudes to health and doctors	Physicians as experts	Data and (dis)information
Social welfare	Collective well-being, social responsibility	Individual well-being, personal litigations
Economic outlook	Higher and more predictable growth	Lower and more uncertain growth