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# **Pharmaceutical Innovation and its Crisis: Drug markets, Screening and the Dialectics of Value.**

## **Abstract**

This article explores the recent debates on innovation in the drug sector, focusing on the ways in which the articulation of use value and exchange value operates in the hegemonic, Northern, form of pharmaceutical capitalism. Engaging with the abundant literature on the crisis of productivity, the paper uses the vast historiography of post-WWII pharmacy to propose a critical understanding of the crisis. It argues that the contradictions resulting in mounting issues of access, expertise and novelty are constitutive of the “screening regime” of invention as it emerged in the reorganization of the sector after World War II. These tensions have just accumulated during the last two decades and become more visible. This leads to a new reading of the present turn toward biotechnology and a more speculative (financial) and economy of pharmacy. In conclusion, the paper insists on the importance of two alternatives to bio-capital originating in the activities of Southern companies: generics and a political economy of access on the one hand, industrialized herbal remedies and a political economy of reformulation regime on the other hand.

**Keywords:** value, bio-capital, crisis of innovation, screening, access, reformulation.

## **Introduction**

In the early 2000s the conjunction of three major events, which were at the same time scientific, economic and political signaled that the Northern “big” pharmaceutical world was in turmoil. The first affair, in 2001, was the opening of the trial opposing the South African government and 40 pharmaceutical companies over the former’s intent to import “generic” anti-retroviral therapies from India in order to combat the devastating local HIV epidemics thus infringing the patents protecting the uses of these molecules and the Trips agreement on

the globalization of intellectual property that South Africa had signed (Cassier 2002). The trial initiated a major mobilization of Aids activists and health personnel internationally. This pressure induced the drug companies into withholding their judicial complain and – later that year – resulted in the Doha declaration, which made explicit that intellectual property rights should not hinder developing countries from using all the flexibilities of Trips to combat public health emergency including mandatory licensing.

Fourteen months later, in January 2003, the US Food and Drug Administration (FDA) issued new guidelines regarding the preparations used for hormonal replacement therapy (HRT) of menopause. According to the FDA, these medications were no longer to be employed for preventive purposes, should be prescribed at the smallest possible doses and never for more than 5 years. These guidelines followed the early termination of the Women Health Initiative, a very large cohort study, which demonstrated higher risk of cancer and cardiovascular disorders among the women taking HRT. This threatened a way of prescribing hormones physicians had viewed as beneficial for more than twenty years (Watkins 2007). The end of the trial opened a public debate about the failure of drug evaluation and regulation whose quick and radical consequence was the fact that women opted out with sales massively dropping in all industrialized countries. In the US, in 2008, sales had for instance been reduced to 10 millions packages instead of 70 millions in 2002.

Third, that same year 2003, *Nature Reviews Drug Discovery*, a new entity in the Nature publishing galaxy targeting experts in the pharmaceutical sciences as well as health economists and industry managers started the publication of articles focusing on what they labeled the declining productivity of research and development in a sector considered as one of the most profitable in the global economy. For the next ten years, the journal thus paradoxically became the favorite publication site for a wave of news, reports and analysis concerned with the actual *absence* of adequate amounts of drug innovation.

These three events each point to different forms of crisis in the drug sector: a crisis of access to essential medicines in the case of HIV with access to medications hindered by intellectual property rights and rules of market construction; a crisis of expertise and evaluation in the case of HRT whose roots were attributed to the massive conflict of interests, that is to say the multiple links between biomedical researchers, elite physicians and the drug companies; a crisis of innovation whose features and origins remain a matter of controversy but calls for more research investments, new targets and modes of product development.

The three crises display different geographies and temporalities. Controversies and scandals have long plagued the therapeutic revolution and the discovery of many new classes of drugs after WWII. It is however only in the last quarter of the 20<sup>th</sup> century - and in the Euro-US space - that their recurrence and systemic roots have become highly visible in the political sphere (Angell 2004). Conversely, the crisis of access has been a permanent feature in developing countries, thus resulting in repeated and usually not very successful attempts to list essential drugs, foster local production, or mobilize international aid. It is only in the early 21<sup>st</sup> century with the marketing of novel antivirals, like sofosbuvir, or novel cancer therapies that patent-based monopoly and high pricing have triggered renewed debates about access and financial sustainability of health care systems in the North (Cassier, this issue).

The conjunction of public discourses regarding problems of access, of expertise and of innovation is therefore a relatively new phenomenon. These issues nonetheless share common roots in the process of *valorization* typical of an industry whose political economy challenges economic neo-liberal orthodoxy since it is bounded to issues of rights and essential needs, oligopolistic modes of market construction, massive in-house research, and multiple forms of regulation (professional, industrial, administrative).

Contradictions in the processes of value making are not specific to the pharmaceutical sector and biomedical economies have recently provided opportunities to go back to thinking with Marxian categories (Dummit 2012, Sunder Rajan 2017). Marx insisted that any proper understanding of capital has to come from beginning the analysis with the question of value.<sup>1</sup> And for capital, value has no meaning unless it is surplus value. For money to be capital, it must have the potential for generating surplus within it as it circulates in processes of commodity exchange. In relation to the situation of European (especially English) industrial capitalism that Marx was writing about, this potential comes from what he called labor power – the potential for the worker to generate more labor than that equated by wage. More generally, Marx provides a methodological insight into how capital generates value *through an exploitation of bodily potential*, even as the generation of value becomes an end in itself. Further, *value is that which allows the commodity, which is always the product of specific and concrete human labor, to figure as abstract labor*. At the core of Marx's critique of political economy is his insistence that *value is an abstraction device*. Therefore on the one hand, value is simply an *attribute* (something that a commodity has: its utility, its beauty, its ability to be worn or eaten as well as something that money has: its ability to circulate itself, to mediate and measure other kinds of circulations, to quantitatively express circulation itself). But on the other hand, within processes of exchange and circulation of capital, *value itself performs the various abstractions of those things that it is supposed to represent*. In other words, the question of value is one that develops its fullest treatment when analyzed in

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<sup>1</sup> Marx writes in *The Grundrisse*: "To develop the concept of capital it is necessary to begin not with labor but with value, and precisely, with exchange value in an already developed movement of circulation" (Marx 1993 [1857]: 259). This does not mean that labor is unimportant; just that one can only understand how it comes to be at stake, alienated and exploited if one begins one's analysis from the question of value.

relation to processes of production and commercialization, the resulting exchange value *tends to render* questions of utility, questions of use value, secondary.<sup>2</sup>

The aim of this paper is to explore the ways in which this dialectics between use value and exchange value operates within the world of drugs and the ways in which it contributes to the crises of expertise, access and innovation, focusing on the latter. The existing literature in STS and political sciences has paid more attention to the former and more generally to the roles knowledge and its production play in the administrative regulation of drugs. It has therefore thoroughly discussed issues of capture, conflicts of interests, ignorance or undone science in order to account for: a) the ways in which the regulatory process, in spite of repeated reforms and public critiques, tend to favor the construction of markets as best means to achieve access (Abraham 2005, 2006, 2007, Angell 2004, Carpenter 2012, Rodwin 2011, 2012); b) the ways in which the industry organizes its marketing operations, especially the multifaceted work invested in organizing clinical trials, in managing key opinion leaders and in marketing proper (Greene 2007, Mirowski 2005, Author 2014, Sismondo 2019).

Anthropologists, given their deep interest in international/global health and local health practices, have more attracted to the crisis of access, analyzing the ways it affects medical work and care. Local responses to the pervading problem of scarcity and access have therefore been center stage with, for instance, the organization of clinical triage, patients'

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<sup>2</sup> This reading of Marx has been influenced by the numerous comments on the discrepancy between the position defended in *Capital* and Marx's early writings, which emphasized a more intricate relationship between use and exchange value associated with the critic of human alienation to commodities and the centrality given to the category of needs. For a thorough discussion see A. Heller, *The theory of need in Marx*, London, Allison & Busby, 1976 and I.I. Rubin, *Essays on Marx Theory of Value*, (English translation), Detroit, Black and Red, 1972 (1928 for the Russian edition) who masterfully show how the notion of alienation was in *Capital* redefined around the contradictions of the production process itself with the salaried worker being the sole actor experienced the dual live of products and goods. A key – and problematic - result of the transition was to relocate the dialectics of value within the production process *without* connections to the construction of markets whose dynamics are – as a consequence - entirely subsumed under the laws of exchange value.

engagement with NGOs and/or the state, the distribution and production of generics (Biehl 2007, Hayden 2007, Nguyen 2010, Peterson 2014).

Taking the crisis of innovation as entry point and engaging with the economics literature that has discussed it for nearly twenty years, this paper is about the two sides of the crisis of innovation, having to do on the one hand with questions of exchange within markets that have historically been capitalized in very specific ways (the financialized, monopolistic capital of the Euro-American pharmaceutical industry); and on the other hand with the question of the kinds of products and the kind of utilities pharmaceutical “innovation” within this capitalized political economy produces. My contention is that these two dimensions, use and exchange, do not simply index separated instantiations of value pertaining to distinct realms of social life, one bound to markets, the other to needs and their fulfilments, but rather resonates with the two facets of drug capital itself.

The paper consists of two parts. Part 1 discusses the crisis of innovation, the discourses identifying its symptoms, and providing a diagnosis for its origins. This critical examination leads into a first contextualization focusing on the recent transformations of the sector and its political economy. Part 2 historicizes the crisis. Building on the recent historiography of post-WWII pharmacy, it proposes that the crisis discourse and the changes it points to are rooted in the long-term contradictions between use and exchange affecting the dominating regime of pharmaceutical innovation, i.e the screening regime of research and development. The paper then discusses the theoretical implications of this hypothesis, including the alternative responses to the crisis drug companies from Southern countries have elaborated.

**1 – The crisis of pharmaceutical innovation: in-house discourses, symptoms, and responses.**

Since the early 2000s, the scientific literature emanating from health economists, pharmacists and industry managers has linked the idea of a crisis of productivity with three types of indicators : the number of New Molecular Entity (NME) approvals, the costs of drug research and development (R&D), and the rates of attrition when a molecular drug candidate moves along the screening pipe-line from to preclinical studies to phase 1, phase 2, phase 3 trials, and finally to market launch.

Approval data are almost exclusively those of the US FDA, the only agency for which we have long-term series on the numbers of applications filed, substances or indications authorized. This has however created a kind of bias due to the administrative reorganization of the agency in the 1990s. The widely circulated figures showing a sharp decline in the number of authorized NME entities in the late 1990s is thus a consequence of the accelerated treatment of a backlog of applications filed in the late 1980s and early 1990s. Even if the data regarding the number of applications filed each year at the FDA are more significant, data regarding “new molecules” have been contested with claims that the crisis of innovation is a kind of myth invented by the industry to legitimize high costs of its products and changes in the legal context (Cohen 2005). NMEs are actually very rough indicators, which for instance say nothing about the intensity of the research effort or the nature of these innovations. Other parameters have therefore been introduced.

The most significant are related to R&D investments and costs. Authors like Booth have for instance computed productivity indicators (in that case the ratio of NMEs authorized to the money invested in research) with all the difficulty of estimated the costs of development (Booth & Zimmel 2004). Existing results then converge to point a long decade decline of productivity (from the mid 1990s to the late 2000s) and a very impressive trend as a consequence of which the costs associated with the launch of one molecule has been increased by 300 to 500 %. This has strongly reinforced the co-related idea of the “end of the



therapeutic revolution”, which links the crisis of innovation with a historical scenario emphasizing the highly successful period of 1945 to 1975 when most therapeutic classes we presently know were renewed or invented, i.e. antibiotics, psychotropic drugs, anti-inflammatory and corticoids, etc. One impressive study in this respect is the one by B. Achilladelis and N. Antonakis published in 2001 (Achilladelis & Antonakis 2001). Taking into account more than 1700 widely used products, they looked at the time of their discovery, their commercial success and their technological similarities. They accordingly identified rupture and cumulative innovations and identified five waves of major products’ introduction. The three most important took place between 1930 and 1980. The study did not point to the decreasing pace after 1990 but, the authors suggest, reveals that the postwar waves of innovation, in contrast to previous ones, were associated with a few giant companies, which all sustained large in-house research infrastructures.

One last type of more refined indicators are attrition rates. These have been computed only for recent periods since they required comprehensive data about the research projects, clinical trials in the first place and their outcome. A widely discussed paper by F. Pammolli is highly illustrative of a pattern that complements the costs figures (Pammolli *et al* 2011). Attrition rates have been on the growing side since the 1990s. The phenomenon is however not so much related to preclinical studies than typical of the human trials, especially those corresponding to phase 3 when efficacy and larger groups of patients are at stake. In contrast attrition rates at the, final, level of registration remained relatively stable and low. Overall rates of success (from phase 1 to approval) are linked to attrition rates since they just summarize the probability that a candidate molecule will reach the market. These have been falling all along the 1990s and early 2000s to stabilize below the 10% threshold (Smietana 2016).

This brings in the question of the interpretative framework. The discussion has brought in many possible culprits for the crisis of productivity, some more temporary than others, some cognitive, others organizational. Focusing on the specificity of the 1990s, authors like Booth have insisted on the nature of the research. Building on the current idea that the industry has then, for reasons to better analyze, refocused its investments on biological macromolecules and biotechnologies, they insist on the fact that these were non-validated targets, meaning were of unproven clinical utility, and were therefore much more risky technologies.

Alternatively, authors like Kneller who are interested in institutional and organizational models have pointed to the wave of mergers and reorganization, which took place in the 1980s and 1990s, suggesting that these changes are both a reflection and a contribution to the fact that the big companies have become very big, increasingly complex if not bureaucratic structures (Kellner 2010). In one word pharmaceutical firms are just “too big to innovate”.

A widely shared idea is however of a different kind. Building on the supposed links between market incentives and innovation, it looks for the changes in the administrative regulatory framework as the main source of difficulties. The idea is supported by data on R&D investments (DiMasi *et al* 2003; Chen 2005) as well as the disaggregated attrition rates. It says that the introduction, growth, and increasingly complex requirements of clinical trials mandated to obtain a marketing authorization have induced the booming costs and rising attrition rates, in turn responsible for the decreasing productivity. In other words, the crisis of innovation is argued for as being consequent to regulatory rather than market failure.

Given that diversity of interpretation, one should not be surprised that the discussion also pointed to a variety of “responses” experimented in the industry. In an unpublished paper, Edward Hughes, managed care expert at Northwestern University, tried to list them in a temporal-complexity order, beginning with the most simple one, putting more money in the

pipe-line, to attempts to diversify the knowledge (and target) basis with biotech acquisition, and finally more fundamental changes of the organizational and economical model with tendencies to externalized R&D or the would-be exploration of an open-source model that would limit the domination of patents as mode of appropriation.<sup>3</sup> Other responses exist, ranging from internal tinkering with the research organization (like multiplying candidates in the early stages of screening followed by more stringent selection in the latter, more costly, clinical stages) to lobbying in favor of regulatory reforms extending the duration of intellectual property rights or creating accelerated evaluation and access to the market like the Orphan Drug Act of 1983. What characterizes this repertoire of responses is therefore a deep inscription in three large transformations analysts have pointed to, namely the rise of biotechnology, outsourcing and financialization.

Sociologists and economists of innovation have looked at the former as example in the creation of a “knowledge economy” (Kahin & Foray, 2006), i.e. in the “commodification” of research through the conjunction of three elements: 1) the emergence of new forms of knowledge; 2) the creation of startups valorizing research results in a more less straightforward way through patenting; 3) the financing of these through venture capital and innovation markets. This transformation would not have taken place without major political and institutional changes.<sup>4</sup> In the US context, the 1980s have thus seen the conjunction of three initiatives: 1) the transformation of Nasdaq into a speculative market for financing innovative firms not (yet) involved in the production of goods or services; 2) the passage of the Bayh-Dole Act to foster technology transfers from the academia; 3) the enlarged practices of patent approval at USPTO, which culminated in the normalization of property rights on genes, cells and entire organisms.

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<sup>3</sup> <https://pdfs.semanticscholar.org/b3b2/3901ff6b8f3726f819d9d6e7336f2a545244.pdf>

<sup>4</sup> For an overview: Gaudilliere, 2015.

This rise of an economy focusing on the early appropriation of biomedical research outputs and their specific valorization has been reinforced by a general trend towards the end of the “research factory”, i.e. the tendency to reduce *in-house* research capabilities. From the late 1980s onward, large firms like RCA, AT&T, Westinghouse and many others started to downsize their scientific platforms to establish networks of partner firms including a nebula of start ups and research organizations (Buderi 2002). A good example is provided by the rise of the CROs and other contractors (Mirowski 2005, Sismondo 2009 and 2018). These may fulfill many functions: prepare articles and follow the process of publication (ghost-writing), organize clinical trials through networks of physicians distributed all over the globe; prepare marketing permit applications and lobby for their approval, etc. This externalization is usually viewed as a mode of costs containment. For instance, in the case of clinical trials the costs of maintaining relationship with qualified physicians, of recruiting patients, of collecting and analyzing data are transferred to CROs, which – in contrast to the previous contractors (clinical services and hospitals) share the same managerial culture and the same criteria of efficacy than the contracting firm. More broadly, outsourcing may be viewed as a new type of value formation breaking with the “chandlerian” structure of large corporations. As such it goes with increasing emphasis on flexibility of tasks, just in time production, and the search for rapidly rotating market niches.

The rise of biotech has also contributed to the financialization of the drug industry but the latter is not simply an effect of the former. Pharmaceutical enterprises are certainly about making (new) drugs but more decisively they are about making profits under the new conditions of an increasingly finance-dominated form of capitalism. Two general trends, which today dramatically constrain the operations of large corporations, are in this respect relevant. The first one is the fact that owners’ rights prevail over all other forms of accountability be it industrial (in terms of material output) or social (in terms of public

responsibility). Major symptoms of this pattern are: a) the fact that the proportion of payments made by US corporation in the form of dividends, interests or buy-backs are arisen from 20% in the 1960s to 60% in the 1990; b) the fact that the proportion of all US equities owned by US private institutional investors has escalated from 12 % in 1960 to 61 % in 2005. The immediate consequence has been a corresponding decline in the capital re-invested and a shift in the balance of power from the engineer-manager of the manufacturing firm to the financial-manager of the trading fund (Aglieta & Rigot 2009). Pharmaceutical industry managers thus operate under the close surveillance of a board of directors who represent exclusively the interests of shareholders. They are more likely to be motivated by the carrots and sticks of stock options, bonus systems and the overhanging threat of immediate dismissal. And the shareholders expectations are increasingly a steadily rising rather than a stable return on equity.

The second trend has been powerfully exemplified by the 2007 subprime crisis and the disclosure of securitization mechanisms. It is a massive rise of intermediation activities based on the multiplication of special vehicles, the creation of new equities through insurance and reinsurance and more generally the shift from banking as a practice of lending to banking as a practice of trading on enterprises bounds and equities. Main symptom of this pattern is the unprecedented discrepancy between the value of production and services as measured by the GDP and the total value of titration by stock markets, which reached a 1:8 ratio for the US economy in 2007 (Mirowski 2013).

Financialization and outsourcing thus seems obey to one single logic, that of an increasing autonomy of value - a value that is, in Marx's suggestive phrase, "self-valorizing" - within processes of exchange and capital accumulation, but also a value that is increasingly speculative. This is reflected in the multiple and dramatic effects of the disjunction between the value created on financial markets and the "real economy", to borrow from the phrase

often used to design the actual production of goods and delivery of services. The multiple response to the crisis of innovation and their roots in the transformation of the drug industry after 1980s however suggest that the new modes of economic valorization are not independent but deeply rooted in the changing nature of drugs' biomedical utility.

This is powerfully illustrated by the changes the last ten years have brought in the discourse of crisis. As K. Smietana and her colleagues at McKinsey observed in 2016: “The topic of R&D productivity in the pharmaceutical industry has been discussed for more than 20 years. It has been largely a story of decline. In fact, around 90% of potential drugs that enter Phase I trials are destined to fail, and for more than a decade we have observed a downward trend. (...) At the level of the industry overall, the decline has now stopped, and for the first time since we started analyzing such data, cumulative success rates are up in the 3 years to 2014, compared with the previous 3-year period. » (Smietana 2016) This more positive perspective has resulted in a sharp decline in the flow of publications discussing the crisis. Research papers and original academic research papers on the topic have for instance disappeared from *Nature Reviews Drug Discovery* since 2014.

The paradoxical nature of what might be mistaken for “the end of the crisis” and its transformation into a historical phenomenon is that the signs of improved productivity, among which the radically increased number of NMEs approved by the FDA (which reached 52 in 2017 from a mere 25 in the 2000s) figure prominently, coexist with the great stability of other crisis indicators. In another paper on their slightly improving productivity index (from a low 0,5 in 2009 to 0,9 in 2014) the same authors remarked: « However, the industry still struggles with high failure rates for investigational compounds, which contribute substantially to the ever-climbing costs of launching a single successful drug. » (Smietana 2015). Authors like Munos or DiMasi keep insisting on the fragile and non conclusive status of these data since the costs of placing one new molecule on the market keeps growing at a fast pace to reach 2,6

billions in 2016 while success rate remains very low, around 10%, having improved of a few percent only (DiMasi 2016).

Moreover, the noted improvements are associated with a few therapeutic classes. The new antiviral and cancer therapies originating in genomics and/or immunology count for half of the products in development and new approvals (Moser 2018). What seems to pay off are therefore less the reorganization of the past twenty years than the massive investments in DNA-based biotechnology.<sup>5</sup> The consequence is that far from resuming with the launch of blockbusters, large drug companies presently try to systematize or – to say the least - test the limits of an economic model based on niche biological products, purchase of startups with promising portfolios and dramatically increased prices paid for by insurances, care providing organizations and patients (Cassier, this volume).

## **Part 2 – Screening, the postwar capitalistic regime of drug innovation and the crisis.**

To bring this engagement with the economic literature on the crisis to a close, one should mention another type of considerations – more historical - that may be illustrated with a widely discussed paper on “60 years of pharmaceutical innovation” (Munos 2009). The first thing its authors did was to evacuate the discussion on number of NMEs authorized, stressing that if one looks to the long term trends at the FDA, apart from occasional blips like the 1996 administrative peak, these numbers have been remarkably stable. Should one conclude that the very notion of a crisis should in consequence be given up? Munos and his colleagues clearly say no, pointing to the escalating costs. The novelty of their analysis is however to argue, on the basis of fragmentary but suggestive industrial data, that this is also a long-term

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<sup>5</sup> An alternative interpretation of the improvements is that they simply result from cost reduction: namely that firms have “cleaned” pipelines and are now being more selective at the preclinical stage, thus reducing the failures due to safety problems but without much impact on attrition due to a lack of efficacy (Waring 2015, Morgan 2018).

phenomenon not a by-product of the last twenty years. Costs started to rise already at the beginning of the therapeutic revolution in the 1950s. Since then they have never diminished and, more importantly, their growth has remained exponential. The dynamics has not been affected by any discontinuity, including major regulatory changes like the 1962 law mandating controlled clinical trials of efficacy. In other words, the declining productivity it is not only old, it seems to have been the “same” since the present organization of drug R&D stabilized in the first two decades after WW2. One may dismiss Munos’ results as too partial and preliminary or take them as proxy for something the recent historiography of pharmacy helps understand, namely the “screening model” of drug invention, which became hegemonic in the 1960s and 1970s.

This opens up the question not just of the economic structures within which pharmaceutical R & D operates, but of the R & D model itself as it has been operationalized. The hypothesis this section argues for is the idea that the problem that is being wrestled with by the in-house diagnoses of a crisis of innovation is not merely the consequence of “external” circumstances like the changes of regulation or (on the critical side) the financialization of late capitalism but an effect of the screening operations *per se*. The internal contradictions, both epistemic and economic, which plagued the screening model of innovation from its early days, have been aggravated with its generalization in the 1960s-80s. It must be noted for the purpose of this discussion that screening should not be taken in its narrow meaning, i.e. the strong coupling of chemical synthesis and pharmacological testing within the premises of the industry, but as a broader regime of innovation performed by Northern pharmaceutical drug companies, which integrates research, production, promotion and sales in a linear pipe-line including clinical trials, scientific marketing, sales and regulation beyond the mere practices of laboratory-centered innovation. That this regime places molecules at its very center goes without saying.



The historiography of post-World War II drug research is best epitomized in the work of H. Marks, I. Löwy or A. Cambrosio and P. Keating, which provide a good understanding of how statistical evaluation in the form of controlled clinical trials emerged in medicine, how the tools of would-be evidence-based medicine were transformed into regulatory instruments by the U.S. Food and Drug Administration (FDA), how this endorsement was unevenly imparted to various fields of medicine, with cancer as the one specialty in which clinical research became such standard practice that trials became a distinctive feature of the care routine (Lowy 1996, Marks 2000, Keating & Cambrosio 2012). This historiography however has to a large extent left out the firms themselves as well as the issue of the links between the trial-culture routine work in medical general practice and mass consumption of drugs. Looking at the practices of value making may be a way to fill this gap, at least from the perspective of the transformation of pharmacy into a full-fledged capitalistic industry.

What historians like S. Chauveau, V. Quirke, J. Greene, D. Tobbell, D. Carpenter and many others in the past fifteen years have taught us in this respect is that the post-war reorganization of the Western world of drug making can be characterized by five main features (Carpenter 2010, Chauveau 1999, Author 2013, Greene 2007, Quirke 2008, Tobell 2011):

- the changing scale of a market increasingly supported by new forms of benefits provided by health insurance, national or private, thus turned into aggregated, collective spending;
- mergers or disappearance of vast numbers of small family-run firms that had originated in pharmacies established by graduated professionals;
- introduction into the market of whole new classes of drugs, opening the door to chemotherapy in areas that had either not at all been working with therapeutic substances (cancer) or not doing very successfully with them (tuberculosis);

- the rising importance of administrative rather than professional or industrial regulations, with as a consequence a significant drop in the number of specialties sold on the market in all major industrial countries;
- generalization of chemical-biological-clinical screening as the dominant path to drug invention, which in the eyes of most firms gave them the possibility of finding radically new active substances rather than copying, modifying and combining those included in the pharmacopoeia, therefore legitimizing massive investments in internal research infrastructures.

What is less often stressed is however that within thirty years this combination radically altered the construction of drug markets and placed the search for ‘innovations’ centre-stage. The idea here is not that research and development were becoming the determinant factor in investment choices or in the generation of economic value. The perspective is rather that the advent of particular structures of pharmaceutical capitalism that brought together innovations in pharmaceutical marketing (Greene 2007, Dumit 2012, author 2013) and models of drug development based in screening and randomized clinical trials changed the nature of market operations, and led to the development of bio-capitalist economies that imagine the articulation of biomedical utility on the one hand, and circuits of drug/commodity exchange on the other in very specific ways. Rather than anticipating development and growth on the basis of competition through prices and short-term management by taking sales data as the major if not the sole indicators, large post-war pharmaceutical companies increasingly relied on monopolistic practices rooted in patent protection, competition for entire therapeutic classes and long-term planning of launches and massive marketing – all strategies that strongly connected with, depended upon and further fed into the in-house screening model of drug invention.

The history of screening can be traced back to the 1920s and 1930s when chemical companies like Bayer, BASF or Rhône-Poulenc radically expanded their catalogue of therapeutic agents. The historian John Lesch has shown how the discovery of sulfonamides at Bayer originated in a new coupling between the chemical division of the firm and its pharmaceutical division; the first one being in charge of producing families of analogs of a given promising structure and the second of testing their properties in animal models *Testobjekte* used to model human diseases and objectify healing potency (Lesch 2006). This is the classical understanding of screening, namely as a process of systematic, industrialized, synthesis of promising chemicals followed by laboratory selection of those showing enough efficacy in experimental systems. The case of the German firm Bayer and its development of sulfa drugs in the 1920s-30s however reveal another dimension. Screening became not only a linkage of chemistry and pharmacology. From the 1930s onward, at Bayer, the selection of new molecules also included clinical assessment of efficacy and economic – profitability - evaluation. The *Werdegang* Bayer managers then proposed to account for all the steps leading to the introduction of a new chemical on the market started with chemistry to finish with economy and law - just like contemporary pipelines.

Screening again changed nature after WW2. One reason was the in-house dynamics of laboratory growth, which resulted in a radical increase of the chemical workforce and consequently of the sheer number of molecules at disposal. The other reason was the generalization and *internalization* of controlled clinical trials. It is not that pharmaceutical firms did not engage in the evaluation of efficacy before WW2. But they did it through long-term collaborations with a small group of elite clinicians who were left free of experimenting in all sorts of directions. Some aggregation and statistical treatment was involved but at a late stage, on the basis of reports focusing on the summary of clinical cases. The 1950s-1960s mounting reference to controlled trials, to double blind procedure, to randomization, to

standard protocols, to statistical control of significance, to collaborative studies led by the industry was therefore a significant change of practices.

Its roots are usually located in the 1962 reform of the FDA. From a legal perspective it is the case that the RCT and the phased trials were turned into regulatory tools in the United States (in contrast to Europe) as response to the thalidomide crisis; a response backed by an alliance of administrators and elite physicians suspicious of the threats large companies and their marketing activities could pose to public health (Marks, 2000; Carpenter, 2010). What was however unexpected is that the passage of the 1962 did not meet any serious challenge from the industry. One interpretation of this absence is that the committee presided by Harris Kefauver, which proposed the reform, was previously investigating prices and patents. The trade off finally passed was thus to exchange an absence of change in the patent law for the approval of mandatory efficacy evaluation by the FDA. This was all the more acceptable to large companies dominating the sector that they were already involved in the organization of trials. Thus, the law mandated something, which was only a significant but manageable displacement of existing clinical activities of the companies.

This industrialization of clinical trials however brought in a new coupling with scientific marketing. Scientific marketing is not publicity. As we have shown, it is different way of constructing drug markets, which relies on two different ways of mobilizing science. The first one is the development of marketing as a research activity based not on only on sales data but, for instance, on sophisticated surveys of prescription practices and motives. The second one is the use of laboratory or clinical research for promotion. This has not been invented in the 1960s but the scale and the nature of this “scientific marketing” radically changed when, after WW2, prescribing physicians became the exclusive targets of marketing departments (Author 2013 and 2015).

A key sign of this change is the 1950s-1970s growth of the prep-representative system, which became the core instrument of scientific marketing. The hundreds later thousands of prep representatives employed in large firms were not only sales agents, they were given special technical training, eventually short stays in laboratories and clinical services. For each product, they were armored with a sophisticated palette of written documents presenting, shaping and interpreting chosen results of laboratory tests and clinical trials.

The rise of scientific marketing was rooted in important changes of organization, beginning with the creation of proper marketing (rather than 'propaganda') departments and the reorganization of their medical homologues out of the qualitative and relatively informal handling of a few dozens long term partners. Clinical research and marketing were thus coupled in new ways with regular exchanges of information. For instance at Geigy in the late 1960s these included a common internal newsletter for the representatives and annual scientific conferences reviewing the status of all molecules in development.

Scientific marketing is a powerful embodiment of the dialectics between use value and exchange value. Its nature and effects may be summarized with a few statements: a) scientific marketing constructs markets through integrated campaigns mobilizing ads, in-house organs, representatives, clinical trials, publications in academic journals; b) it is an integral element of the post-war screening model of drug development from systematic chemical synthesis to market research; c) it creates prescription practices, which do not simply respond to medical needs but define them; d) it registers medical practices, including contests and failures, triggering changes of products and recommended indications; and finally e) it displaces the norms of intervention and redefine the boundaries of diseases.

Taking the case of the Swiss firm Geigy, which became famous for its development of psychotropic drugs in the 1950s-60s, the juncture between the creation of exchange value and

the construction of use value may be illustrated with the company's search for the big "antidepressant". In the late 1950s, Geigy had developed Tofranil, the first psychotropic drug whose effect on depression was not envisioned in screening but discovered in the clinic, by psychiatrists tinkering with Geigy's recommended indications. However, this remained a limited market, for severe depression, treated in hospitals while the big and rapidly growing market was that of tranquilizers. By the late 1960s, the firm was therefore looking for an antidepressant, which could occupy the ambulatory market and occupy the niche of "a first efficient tonic". The proper molecule was finally found in the early 1970s. Ludiomil's launch campaign thus focused on a new clinical category – masked depression - whose definition and boundaries as a widespread and mild form of the disease, which could be handled by general practitioners prescribing Ludiomil and its parent molecules, was intensively worked out by Geigy's clinical department, its collaborating prominent Swiss and German psychiatrists and a few general practitioners (Author 2016).

Why such organization and commitment to chemistry may finally hinder innovation understood as therapeutic advances rather than simply bringing new molecules on the market?

Most reflections on the limits of the model revolve around the idea that screening has made the relationship between the selection of valuable molecules and clinical knowledge problematic. One may thus distinguish three layers of argumentation that are invoked when screening comes under the critical scrutiny of physicians and other actors in drug innovation:

- 1) The epistemic problem - Screening enables investigations centered on bio-molecular properties and modeling giving secondary roles to clinical knowledge and care experience.
- 2) The organizational problem - The screening pipeline is a linear 'lab to the hospital' organization. It does not facilitate "feedback" while standardized protocols marginalize clinical tinkering and routine practices.

3) The economic problem – Scientific marketing is an integral part of screening and enhances the selection of “incremental” molecular innovation and enlarged indications rather than “rupture” innovations.

The idea that the contradictions of screening constitute the backbone of the changes the discourses on the crisis of innovation refer to is both tempting and challenging. One should make clear that our the screening hypothesis: 1) takes seriously the idea that the pharmaceutical industry has in the past three decades faced mounting difficulty in finding and selling new molecules without endorsing the prevailing discourses on the crisis and their market-centered ways of understanding innovation; 2) is not a new version of technical determinism stating that the technology of screening (first of all its reliance on chemical synthesis) has finally exhausted its potential; screening is socio-technical system as well as the accumulation of tensions characterizing its historical trajectory.

The screening hypothesis has thus intertwined theoretical and historical benefits. First, in terms of temporality, one may remark that the history of the screening model fits the chronology of the crisis the “productivity” studies propose. Geigy is thus typical of the majority of postwar rapidly growing firms, which – in contrast to Bayer – did not organize their research on the basis of full-fledged screening before the late 1960s or the early 1970s.

Second, the screening hypothesis sheds interesting light on the changing targets selected in the R&D practices of the industry. Analysts have documented the mounting importance taken by the pharmaceutical management of health-related risks, cardiovascular as well as psychiatric ones (Aronowitz 1999, Dumit 2012, Greene 2007) in the late 20<sup>th</sup> century Northern drug markets. This form of intervention has provided for an important part of the sector’s growth in the 1980s and 1990s through massive investments in the redefinition of disease boundaries and the correlative transformation of risks into entities that must be

handled as if they were already pathologies. In terms of research, the gradual saturation of this dynamics has increasingly resulted in the emphasis placed on the so-called “me-too strategy”, namely the development of a vast palette of molecular variants from a few and already old “head of series”. Me-too show relatively similar clinical properties than the substances used as reference. Me-too are however not simply “me-too” that is to say faked innovations introduced for the purpose of maintaining market shares and controlling exchange value. Me-too developments display a more complex relationship to the dialectics of use and exchange. They indeed reflect an absence of clinical breakthrough (thus exemplifying the crisis) but they also very often entail significant change of medical practices (something poorly visible in the screening idiom). Their added value has therefore often been defined in terms of more convenient conditions of use or decreased adverse effects even if – and this may be considered as another symptom of crisis – public controversies have regularly undermined the claims associated with 3<sup>d</sup> or 4<sup>th</sup> generation blockbusters as the early 2000s HRT affair mentioned in the introduction reminds us.

Third, as mentioned above, when aggregated industry investments are taken into account, this strategy of making new wine out of old grapes is not the preferred response. Since the mid-1980s, biotech has been the most favored venue to restore the declining productivity of in-house R&D. The massiveness of this pattern (in comparison with other forms of responses to the crisis of productivity) may be understood as the conjunction of two powerful incentives respectively linked on the one hand to “use” as defined in the screening model, i.e. identify radically new molecular targets and control the clinical through biological rather than chemical lenses, and to “exchange” on the other hand, i.e. secure financial returns by participating in the highly promising juncture between the knowledge economy and the speculative economy out of which biotech – as a frontier market – emerged. One of the most salient evidence in favor of an analytics trying to mobilize this dialectics of use and exchange



to explore the “crisis of screening” hypothesis is the fact that the most recent pay-offs of these investments are associated with a few specialties, for the time cancer and disorders of viral origins. The latter builds on the successful trajectory of ARVs and HIV, relying on the relative simplicity of such infectious agents and of their mode of replication. The former reveals the limits of the screening model since oncology has been – since the 1960s and the rise of cancer therapy – one of the few biomedical domain for which a majority clinical trials have been financed with public money (from the NCI in the United States) and conducted in integrated cancer research centers with the consequence that many of these trials have focused on treatment *regimens* rather than isolated molecules (Keating & Cambrosio 2012).

This contrasts the more reductionist perspectives, for instance gene therapy, genomic research favored. The new ways of valorizing knowledge in the biotech regime have indeed created situations of major disjunctions between exchange value and use value resulting in the same sort of “bubbles”. A paramount case was, in the second half of the 1990s, the creation of hundreds gene therapy start-ups (Martin 1999) and their subsequent collapse in the mid-2000s when, confronted to recurrent difficulties in translating laboratory promises - often based on the use of genetically modified animal models - into human clinical trials results, the investors’ faith in ADN “blockbusters” vanished. Such developments suggest that changing the targets from chemical to biological molecules does not necessarily alter the linear and reductionist logic inherited from screening and the difficulty to integrate clinical work and care. The renewed crisis in the construction of use value was all the more quickly translated in a collapse of these companies’ exchange value that, up to late 2000s, the overall promise of biotech was long lasting.<sup>6</sup>

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<sup>6</sup> The number of products (or services) and the value attached to them are far from nil but – after 30 years of investments - they were not matching (not even replacing) classical pharmaceuticals and their markets: for the US in 2012 the total value of sales was 63 billions

A fourth element is that the limitations of screening may account for several phenomena the discussion on the crisis of innovation has pointed to, beginning with the high rates of attrition at the clinical stage or the mounting discussion on so-called “efficacy-effectiveness” gap. The latter is the way in which regulatory agencies like the FDA or EMA target the major differences between the efficacy of a given drug as it is objectified in controlled trials and the effectiveness of the same compound when it is used in routine practices under normal, meaning average, conditions of prescription and in association with basic care rather than the exceptional means available in frontier research hospitals.

In a recent paper, Clementine Nordon and her colleagues of the “GetReal consortium” remind us that efficacy/effectiveness gap is not a recent notion, that its presence can be traced back to the “therapeutic revolution” of the 1960s when controlled clinical trials became the object of academic consensus. The gap has, however, in the past ten years enjoyed a novel visibility and its discussions reveal several meanings often labeled “biological” and “behavioral”. The first and oldest paradigm is the idea that the gap is the consequence of “real” differences with the experimental situation meaning that “real life” is messier than controlled life (Nordon 2016). The first keywords in this vision is “adherence” as a way to point to the poor behavior of patients who do not follow the proper pattern of drug intake, associated actions and mandated reporting but also live in a medically complex world where drugs are not isolated and interactions with many therapeutic objects dominate. The second keyword is “poor prescription practice” or physician’s behavior usually perceived as an information problem, the effect of guidelines poor dissemination, lack of time for ongoing education rather than the consequence of complex interactions with patients, industry representatives or fellow physicians.

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for biotech compared with 326 billions for the classical pharmaceutical market. See US Pharmaceutical Industry Statistics. [www.statista.com](http://www.statista.com), last accessed December 2018.

The second and more recent paradigm, closely associated with the discourse of crisis, is the notion that the efficacy/effectiveness gap is the manifestation of epistemic problems in the design and conceptualization of trials. In other words, per design RCTs are not generalizable. They rest on the ability to simplify and control the treatment situation in order to maximize the visibility of what can be attributed to the sole presence of the chemical to be tested. Therefore they oppose the non-controlled care situation in many ways: 1) patients bodies are selected in less stringent ways, they are less homogeneous in terms of medical history, age, genetic background, metabolic patterns, life style, etc. 2) the treatment situation is not optimized in the same way: co-medication are numerous and poorly controlled, access is not always possible, complementary interventions optimizing effect are not available or even thought of.

These two paradigms are intimately related to the responses that have been invented in order to address or to bridge the gap. The prevailing mode of management is to change the treatment situation and align it on the experimental space. Enforcing compliance is therefore not the one-fix-all response to the gap. Epistemic tinkering, i.e. introducing changes in the trials machinery in order to improve their ability to model the care situation and to predict real life outcomes and anticipate solutions, has become the most favored alternative, resonating with critics of the phase 3 trials coming from the industry and backing the idea of early commercialization and more systematic phase 4 observational studies.

Our final comment is that all the responses to the crisis of innovation discussed in the economic literature originate in Northern companies and seek to rejuvenate a political economy of drugs, which has not only been dominated by the screening pipe-line but also by the systematic use of patents as basic infrastructure of valorization. This leaves out a critical dimension of the contemporary configuration of the sector, namely the fact that there are several forms of drug capitalism competing on the global markets. Drug companies from the

South have actually become major producers and actors. They address the problems of valorization in their own way, inventing responses to the problem of productivity, which significantly contrast those of their Northern competitors, relying on two alternative approaches of the dialectics between use and exchange.

The first one is the well-known development of local production and the rise of a large generic industry, first of all in China and India, which are now responsible for the production of a majority of the active ingredients used worldwide (Chaudhuri 2005). Generic drug capitalism does not challenge the screening model since it relies on the same chemical/molecular paradigm. It nonetheless provides for alternative forms of valorization since it does not rely on patents but rather tend to suspend, if not abolish, them in order to foster innovation through copying (Cassier & Corea 2009).

The problem of biomedical utility however does not disappear, and becomes another target for alternatives – one that gets most forcefully critiqued not by generics industries, but by traditional medicine, which operates out of a different epistemology of therapeutic intervention. The best exemplification of this second register is the radical transformation, which affects, for more than two decades, the Asian traditional medicines through a complex process of industrialization. The reformulation of classical combinations of medicinal plants described in centuries-old reference texts lies at the heart of this process. As anthropologists have shown, in the case of Indian Ayurveda, this reformulation means at the same time simplifying and standardizing poly-herbal combinations in order to (1) adapt them to mass and mechanized industrial processing; (2) mobilize elements of biomedical experimentation in the laboratory and the clinic to provide evidence of medical value, and (3) link Ayurvedic and biomedical categories to address the health needs of cosmopolitan consumers (Pordié 2014). The dialectics of value underlying this transformation and the Indian path to bio-capital it reveals is especially visible when the creation of markets articulates the creation of

neo-traditional Ayurvedic formulas and the care of biomedical disorders; for instance the invention of plant-based formulas competing with HRT for the management of menopause and its risks in the wake of the 2002 crisis mentioned in the introduction (Author 2019). This reformulation regime is an epistemic “Southern” alternative to the crisis of innovation.

## **Conclusion**

In a recent article on “Species of Bio-capital,” Stefan Helmreich mapped the various strands of work associated with this notion, making a useful distinction between two lineages, which he calls “Weberian Marxist” and “Marxist feminist” (Helmreich, 2008). The former line of inquiry places a strong emphasis on commodification as a process creating value through market operations. Bio-capital is then a bio-economy characterized by its integration into the financial economy through the typical cortege of patents, startups, stock appreciation. The latter places a strong emphasis on issues of reproduction and life, defining bio-capital as a form of value making that is less rooted in production patterns and labor organization, than in a political economy that involves isolating and mobilizing the primary reproductive agency of body parts and other entities extracted from living beings. These two lines of interpretation strongly resonate with the two sides of bio-capital this paper targets, namely the bio and the capital of bio/capital.

The basic contention grounding our interest in the ways in which the crisis of drug innovation has been discussed, defined, evaluated and responded to in the past twenty years – is indeed that such conversation between economists, managers, and policy-makers provides a remarkable entry point into the contradictions underlying the present dynamics of pharmaceutical capitalism, or to be more specific, the peculiar dialectics between use value and exchange value at stake in drug capital self-valorizing activities.

Taking into account the vast historiography of 20<sup>th</sup> century pharmacy, we have therefore suggested that the multiple tensions resulting in the lack of innovation are constitutive of the “screening regime” of invention as it emerged in the reorganization of the sector after World War II. These tensions have just accumulated during the last two decades and become more visible. Our screening hypothesis is therefore a plea for historicizing the so-called problem of productivity as well as a way of inscribing it in a Marxian understanding of the interplay between use and exchange value.

Those who have thought about value in relation to health have indeed emphasized the interplay between value as legitimized by utility and inscribed in the dynamics of use on the one hand; self-valorizing in the course of exchange and reproducing capital on the other hand. Catherine Waldby’s and Melinda Cooper’s elaboration of the concept of clinical labor, for instance targets the labor of experimental subjectivity, and of reproductive work in the context of new reproductive technologies, as providing new forms of exploitable bodily potential for bio-capital (Cooper & Waldby 2014). In *Pharmocracy*, Kaushik Sunder Rajan explores the dynamics of pharmaceutical innovation, capital formation and regulation in India, following two configurations of political conflicts over health and its appropriation. Several aspects of Gramsci’s approach of hegemony are taken on board to explore the question of value: a) its deeply political nature and roots in “common sense”, which means that valorization is not simply economical but entails multiple cultural and moral layers articulated in different *values*: financial, philanthropic, constitutional, or postcolonial; b) the “intellectual work” grounding hegemony in processes of pragmatic and highly contextual co-production of knowledge, values and politics; c) the decisive contestation taking the form of public scandal, engagements with the law or economic competition, and revealing alternative forms of value making.

Both Rajan and Waldby and Cooper locate value as a process of valorization through the exploitation of the tensions between the satisfaction of socially recognized needs (utility) and the valorization of capital through the processes of exchange (profit). The analysis presented here follows a similar path. The crisis of innovation must be located as a function of the innovation machinery responsible for the valorization of pharmaceutical investments (financial as well as epistemic) – and not, as in-house diagnoses of the crisis suggest - as function of “external” factors such as regulation and state intervention.

In addition to intellectual property rights, the historiography of 20<sup>th</sup> century drug making helps identifying two major nodes in the post-war screening regime where biomedical utility and commercial exchangeability have been closely articulated to become points of high tensions: administrative evaluation and scientific marketing. Both heavily rely on phased clinical trials as dominant mode for framing proper uses, meaning both acceptable and formally sanctioned prescription and consumption practices. In both instances, a specific loop links the work invested in the objectification of drugs’ properties and medical utility and the construction of markets. In other words, exchange value helps prioritize and establish hierarchies between drugs and indications, thus “making” use value while laboratory and trial results, i.e. use value as defined by companies and their patterns helps prioritize and establish hierarchies between markets, thus shaping production and pricing patterns.

Indeed, this is recognized in the critiques of the hegemonic model that are articulated by generics producers, relying as the screening regime does on monopolized markets and the violent enforcement of what may be called a “politics of the copy” – materializing in global trade agreements, global health programs and an increasingly securitized global policing of pharmaceutical circulation (Cassier & Corea 2009; Hayden 2007; Peterson 2014). But, as this paper argues, this only speaks primarily to the dimensions of exchange, to the “capital” of bio-capital. Biomedical utility too is an ingredient to the crisis of innovation: bringing back

bracketed questions of ontology and use is integral to the alternative to the bio- of bio-capital, the industrialization and the globalization of Asian traditional medicines is offering.

Neither critique exits bio-capital – indeed, generics companies are quintessential capitalistic actors themselves (though they tend to operate through the free market as opposed to monopoly markets, and often operate in less speculative modes and environments than “big pharma” does) while Ayurvedic producers are positioning themselves, through their emphasis on the traditional nature of their remedies, as strategic market players. But taken together, these critiques, and the alternatives they propose – even as they are not alternatives *to* capital – make explicit the different pressure points in pharmaceutical value. This might provide us ways to understand the crisis of innovation both as it materializes in high drug prices and questions of access and as it materializes in the lack of adequate products of medical necessity.

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