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A research agenda on valuation processes and markets for medicines

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Introduction

The stakes around the global and national medicines[1] markets have been rising steadily for the last twenty years. From the controversies over patents surrounding HIV treatments and the right of developing countries to infringe these patents and develop generic copies in the late 1990s ('t Hoen 2002; Coriat 2008), to the current debates over the exorbitant prices of certain medicines and the sustainability of the expenditure they generate for national health insurance (Vogler et al. 2016), or, in the current context of the Covid-19 pandemic, over supply disruptions and struggles between countries to access treatments, tests, and protective masks – medicines and health products raise a series of fundamental questions. How can one think of a market in which there operate companies that rank among the most capital-intensive and profitable, states that want to provide their populations with access to essential and innovative treatments without jeopardizing their national health insurance systems, and health professionals who play a central role as market intermediaries? How can one analyze a market in which there exist both innovative medicines (most often but not always) resulting from long R&D processes, protected by patents, and costing up to several hundred thousand euros per patient, and generic medicines, produced on a large scale to treat "common" diseases and costing just a few euros?

These two main questions have structured my research agenda over the last fifteen years. A first line of research is to examine the organization and regulation of health product markets. Drawing on the sociology of organizations (Friedberg 1993; Bergeron and Castel 2016) and the sociology of markets (Dobbin 1993; Fligstein 2002; Beckert 2009; Cochoy and Dubuisson-Quellier 2013), I analyze the general characteristics and specificities of these markets. At a first level, I am interested in the central role played by the state (and its expertise agencies) in these markets. The state intervenes at all levels of the market: in the regulation of market access (marketing authorization procedures), the financial regulation of health care expenditure (reimbursement procedures and even administrative price setting in France), and finally in industrial policy (financial and administrative support for research and development, production and employment). At a second level, I am interested in the dual organization of the pharmaceutical industry (reminiscent of others such as the garment trade). There are both Big Pharma companies that have adopted a productive blockbuster model centered on the financial and market valuation on a global scale of a few molecules with high (therapeutic and economic) added value (Montalban and Sakinç 2013), and generics companies whose business model is based on the large-scale marketing of low-cost and low-price copies (Nouguez 2017). Finally, it is not possible to think about the market for health products without taking into account the role of health professionals, particularly physicians and pharmacists. These professionals are market intermediaries (Cochoy and Dubuisson-Quellier 2013), who ensure, via their prescriptions, that suppliers (industry) meet consumers (patients). But they are also market makers, through their role in the construction of supply (organization, implementation, and evaluation of clinical trials; production control), demand (prescriptions for patients, and promotion and recommendations to other healthcare professionals), and market regulation (expertise in health agencies). This combination of a highly capital-intensive supply, high levels of state control, and strong professional regulation makes the medicines market unique.

The second line of research is in keeping with the rapidly growing field of valuation studies (Boltanski and Thévenot 2006; Vatin 2009, 2013; Stark 2011; Beckert and Aspers 2011; Helgesson and Muniesa 2013; Zelizer 2013). Of the different meanings of the term, I take up Vatin's (2013) conceptualization, which distinguishes within valuation processes *evaluation*, which consists in assigning (economic, aesthetic, moral, health, etc.) values to a thing, a person, a rule, or an action, and *valorization*, which consists in bringing a gain or a loss in value *(devalorization)* to that thing, person, rule, or action. In the case of medicines, I explore more specifically two dimensions of valuation.

In line with the numerous works on product classification and qualification (Bowker and Star 2000; Karpik 2010; Beckert and Musselin 2013), I analyze the actors, devices, and processes that have led to the distinction between medicines and other products (especially food and drugs) and that contribute to establishing their value compared to others. I am particularly interested in the production and uses of the medicines' indications (authorized uses), the risk/benefit balance, and the material and practical dimensions of medicines (packaging, galenic formulation, etc.). These valuation operations do not concern only the medicines but, through them, the manufacturers who produce and market them, the health professionals who discover, assess, or prescribe them, the patients who consume them, and the states that authorize, reimburse, or even price them. In addition, I am interested in the market and financial valuation of medicines through the setting of their prices (see also Doganova 2015). One of the peculiarities of the medicines market is that it gives rise to considerable variations in prices over time and space. Depending on the country or the period under consideration, the same medicine may be sold for a few euros or several hundred thousand euros due to variation in the structure of supply (monopolistic or competitive), of demand (covered by a public health insurance system, a private system, or the individuals themselves), and the mode of state regulation (controlled or free prices). However, these prices also reveal different methods of arbitration from one country to another between three potentially contradictory objectives: allowing access to treatment for all patients; controlling the level of expenditure (public or private) on medicines; and encouraging industrial development (R&D, production, employment). There is, therefore, no reason to separate the analysis of the morphology of the market from that of medicine valuation; the two dimensions interact with each other. To take an example, the marketing of a new treatment considered by experts as making a major therapeutic contribution (for example, Hepatitis C treatments) may place, at least temporarily, the laboratory selling it in a quasi-monopolistic position on the market and result in a high valuation of this product in terms of both price and sales. The marketing of me-too medicines (with the same indications but a more or less different active ingredient) or generics, with the support of the state, can then threaten this position of the laboratory and lead to a spectacular devaluation of the product, with the laboratory losing most of its market share in the space of a few weeks.

In order to understand market organization and medicine valuation, I follow the products in the different arenas where they circulate: the scientific arena, regulatory arena, industrial arena, health professional arena, and consumer arena. I conduct interviews with the key actors in these arenas and analyze the documents they produce or rely on in the course of their activities. But to put these processes into perspective and measure their effects, I also use databases of prices, sales, or consumption. Finally, my research starts from the French market but has progressively extended to the European and global scenes in which it is deeply embedded, although it retains some peculiarities (e.g., the ratio of medicines per inhabitant, state control on prices).

The purpose of this article is to present this research agenda, which is both individual and collective. Readers interested in one of these projects may refer to the bibliographical references for further details.

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Standard equivalence versus status hierarchy: the French market for generic medicines

My first research focused on the creation and organization of the French market for generic medicines (Nouguez 2017).[2] At the beginning of the 1990s, these cheaper copies of original medicines whose patents had expired were virtually absent from the French market. Thirty years later, they account for nearly one out of every three medicines sold, although France remains far behind Germany (80 percent) or the United Kingdom (83 percent).

Three major findings emerge from this study. First, I have shown the central role of the state in the creation and regulation of this market. The state has constructed from scratch what I call "administered price competition," with three main instruments: the legal definition of generic medicines (1996), which established the rules of (bio)equivalence between brand-

name and generic medicines; the administrative setting of a "competitive" price that simulated free price competition through the application of a discount to the price of the original medicine, which has increased as the market has developed (from 20 percent in the 1990s to 70 percent today); the mobilization of pharmacists through the introduction of a right of substitution (1999) and more advantageous remuneration on generics, and to a lesser extent of physicians through performance bonuses and patients through partial reimbursement (of the price differential between original and generic) or deferred reimbursement (if the substitution is refused).

I have then shown that the development of the generics market was based on a new alliance between pharmacists, generics manufacturers, and the national health insurance (NHI) around a principle of generalized equivalence between medicines (the copy is equivalent to the original), manufacturers (the generics manufacturer is equivalent to the brand-name manufacturer), health professionals (the pharmacist's prescription is equivalent to that of the general practitioner, which is equivalent to that of the specialist), and patients (the cancer patient is equivalent to the angina patient; the rich patient is equivalent to the poor patient). This new alliance has come up against the old alliance between originator companies and doctors (particularly specialists) based on a principle of hierarchy of medicines (according to their novelty, their therapeutic contribution, and their practicality of use), pharmaceutical companies (according to their alleged investment in R&D), health professionals (according to their degree of specialization and expertise), and patients (according to their morbidity level and in part to their ability to pay for any non-reimbursed additional medical fees). The French generics policy has been a real professional and economic booster for the pharmacists who have proven to be a reliable ally of the public authorities in raising the substitution rate (measuring the share of generics medicines among substitutable medicines) to 85 percent and generating several billions of economy in twenty years, and who have been rewarded with higher margins and rebates from generics companies and with new contractual prerogatives with the NHI (such as vaccination in pharmacies, pharmaceutical consultations with chronically ill patients, etc.). But it also highlighted the resistance of French (especially specialist) physicians to integrate medicine costs into their prescription choices and their dependence on the originator industry for information and training. The competition between generics and brand-name medicines has therefore been based not so much on price, as economic theory would suggest, but on the ability of statutorily dominated actors (pharmacists and generic manufacturers) to nibble away, with the support of public authorities, at the barriers erected to equivalence by the statutorily dominant actors (physicians and companies selling brand-name medicines).

Finally, I have statistically analyzed the distribution of generics in the different regions of France. I show that this diffusion has been strong in regions where morbidity levels and income inequalities are low (low differentiation of the care demand) and where the density of health professionals is low and their fees rarely exceed the rates reimbursed by the NHI (low differentiation and low concentration of the care supply). Thus it is where the health system is most organized according to a principle of standardization of care supply and demand that the principle of equivalence of medicines is accepted. Conversely, in regions where care demand and supply are the most differentiated and hierarchical, the generics have faced strong resistance from both (specialist) doctors and (high social class) patients. Taking up Bourdieu's concept of structural homology (Bourdieu 2000), I explain this unequal diffusion by way of a homology between the fields of pharmaceutical companies, health professionals, and patients. A patient who is well-off or has a high degree of morbidity is much more likely than a patient from a working-class background or with a common disease to consult a specialist doctor who charges extra fees and is much more likely than a general practitioner practicing for the agreed tariff to maintain strong links with the brand-name companies and weak links with the national health insurance, and to prescribe original non-substitutable medicines rather than their generic equivalent.

As such, generic medicines appear to be the perfect site to study the tensions in the French healthcare system between the promotion of universal access to the same quality of care at minimum cost and the hope or fear of two-tier medicine that would allow some people who can afford it to access "better" care while the others have to settle for poorer medicine. It does not matter much in the cases of generic and brand-name medicines, as they have the same outcome for health (but not for NIH expenditures). But it is much more problematic when it comes to medical interventions, such as surgery, that are less standardizable.

At the boundaries of medicines: markets for cannabis and probiotics

After having analyzed the construction of the French market for generic medicines as a process of internal differentiation through equivalence and price compe-

tition, I turned my attention to the external borders of the medicines market by analyzing two emblematic "boundary products": cannabis and probiotics. Both products entail considerable "boundary work" in which the different actors involved (regulatory authorities, industrialists, scientists, health professionals, and consumers) try to qualify and value them: Are they medicines intended to treat diseases, or health products supposed to maintain health and prevent disease, or even products intended for well-being or recreational use? How do they acquire a health value (benefit-risk balance, scientific evidence, or clinical experience) and an economic value (costs, prices, profits, taxes, etc.)? A second set of questions concerns the organization of the market(s) to which this boundary work leads: What are the rules for accessing the markets (marketing authorization, control over promotion and claims, etc.)? What are the modalities of distribution on the markets (professional control of pharmacists or doctors; distribution by retailers or supermarkets; direct sale to the consumer)? Finally, what are the devices for competition or, conversely, for monopolization allowed by this boundary work (patents, product differentiation, marketing authorizations, etc.)?

I first discussed these various issues in an article, co-written with Henri Bergeron, on the contested market for cannabis (Bergeron and Nouguez 2015). Our article seeks to outline the contours of three main forms of (dis)qualification of cannabis and their corresponding market organization. We deal first with the prohibition of cannabis that still serves as the normative basis in international treaties and for an important number of countries, despite movements in national/regional legislations toward legalization in several countries and (American) states. In this specific legal context, cannabis is qualified as a narcotic having no therapeutic benefit or scientific value and a strong risk of abuse; market regulation operates through a complete formal prohibition on its possession, use, production, and sale; in response, the cannabis trade develops in the shadows, that is, against the state (police repression) as well as outside the state (no legal regulation). We then turn to policies and practices of "risk reduction" and de-criminalization (to be distinguished from legalization[3]) of cannabis use, which have developed in Europe over the past twenty years or so. In this context, cannabis has been (re)qualified as a "soft drug" whose use, though still formally prohibited, is tolerated in practice; market regulation entails varying degrees of tolerance for possession and use, coupled with more stringent repression of production and sale; the cannabis trade then develops in the "grey areas" (such as the Dutch coffee shops) between tolerance and prohibition. Lastly, we study the development of the legal cannabis trade for medical and, most recently, recreational use. In this last approach, cannabis is qualified as a "medical treatment" or a "recreational substance," which may and indeed must be effectively regulated by the state and/or the medical profession; market regulation thus involves the development of rules regarding the characteristics of cannabis and its "acceptable" modes of production, circulation, and consumption, as well as the modes of appropriating the economic profits that such markets may generate.

The second research project, which I am currently developing with Henri Bergeron, Patrick Castel, and Solenne Carof, aims to address boundary products *par excellence*: probiotics. Probiotics were defined in 2001 by the WHO and the FAO as "a living micro-organism which, when introduced in sufficient quantity, produced beneficial health effects for the host." The principal components of probiotics used in the industry are lactobacillus and bifidobacterium. In the early 2000s, these products were sold throughout Europe in four different markets with four different statuses: medicines, medical devices, food supplements, and food with health claims. These products have thus reopened the boundary erected over the course of the twentieth century between the markets for medicines, whose primary function is to treat the sick, and those for staple foods, whose primary function is to meet the nutritional needs of healthy people (Carof and Nouguez 2019). They raise many issues for regulators, producers, distributors, and consumers. Are they health products that can usefully contribute to the prevention or even cure of chronic diseases, or marketing manipulations that are of no health interest? Should they be regulated and marketed as medicines, as food, or as a separate category?

Our research addresses two complementary objectives. Firstly, we are interested in the boundary work carried out by the regulatory authorities (European and national governments; European and national food safety agencies; European and national medicines agencies) to handle what were seen as regulatory overflows. While nutritional and health claims on foods and food supplements were flourishing because of different and often lax regulations in different European countries in the early 2000s, the European Regulation 2006-1924 of December 20, 2006, created a harmonized regulatory framework for the entire common market. First the regulation created a new boundary between food and medicine, having essentially to do with the kinds of claims made by the products: with medicines comprising any product claiming a curative effect on illness or on bodily dysfunction; and healthy foods and dietary supplements including any product claiming a preventive effect (on the risk of illness) or an effect on the maintenance or development

of bodily functions. Then, it also initiated a procedure for evaluating these health benefits. It assigned to the European Food Safety Authority (EFSA) the role of studying and issuing opinions on the scientific bases for all claims submitted by member states. Based on these opinions, the European Parliament was to adopt, by 2010,[4] a positive list of all the nutritional and health claims that could be used by industry actors in the advertising and packaging of their products. Any claim not appearing on this list would be prohibited. To the astonishment of companies, the EFSA revealed itself to be particularly demanding, since only 510 claims out of 2,758 (created through the consolidation of nearly 40,000 applications submitted by member states) received positive opinions at the end of the evaluation process in 2010. As for probiotics, the EFSA rejected all thirty-nine applications, and Danone, one of the major companies promoting food with probiotics, withdrew its application before the end of the evaluation, fearing a negative opinion that would affect its products' reputation. In the same way, the EU Regulation 2017-745 of April 5, 2017, explicitly excluded "viable biological material or viable organisms, including living micro-organisms, bacteria, fungi or viruses in order to achieve or support the intended purpose of the product" from the scope of medical devices. Companies wishing to continue to market probiotics must now comply with the European Medicines Agency (EMA) or EFSA requirements for evidence-based medicine by investing in expensive clinical trials.

We also analyze the boundary work of industrialists and distributors in response to these new regulations. Two alliances of industrialists and scientists have formed to try to co-construct, with the regulatory authorities, the rules for evaluating probiotics in the field of pharmaceuticals (Pharmabiotics Research Institute) or foods (International Probiotics Alliance Europe). Both alliances seek to specify not only the technical characteristics of their products but also the level and methods of scientific proof required for the recognition of these products by their respective regulatory authorities. The regulatory division of labor between the EMA and the EFSA was then mirrored in the division of labor between companies that continued to hope to be able to modify the evaluation criteria and the opinions of the EFSA on health claims and others that considered the EFSA opinions to have definitively blocked the institutionalization of markets for probiotic food with health claims and decided to develop medicines and look toward the EMA. Producers of food supplements and ingredients seemed to still hesitate between the two strategies and thus participated in meetings and conferences organized by these two groups of producers. At the same time, many manufacturers continued to rely on regulatory loopholes to maintain or even increase their sales. This is particularly the case in the food supplement market, where manufacturers have combined probiotics with ingredients (vitamins, minerals, etc.) bearing recognized nutritional or health claims, to maintain the health labeling of their products. These companies have also strongly invested in promotion to doctors and pharmacists who are not concerned by the regulation on health claims, so that they "prescribe" probiotics to their patients.

The aim of this research is to analyze the way in which medical innovation is constructed at the boundaries of regulation in a joint effort by regulators and manufacturers to blur, shift, circumvent, or strengthen the boundary between medicines and health products (Bergeron, Castel, and Nouguez 2013). The research is still in progress and should be extended to a global project in the coming years with the creation of an international network of researchers working on boundary products between food and medicines (Frohlich 2019).

Pricing health: administrative setting of medicine prices in France

A third set of research interrogates the way markets are regulated by central agencies or public administration. Our initial research, conducted in collaboration with Cyril Benoît, focused on the pricing of reimbursed medicines in France (Nouguez 2014; Nouguez and Benoît 2017). We studied the successive forms of this policy, from unilateral state administration of prices, in effect from 1948 to the 1980s, to price negotiation in the framework of agreements between an interministerial committee (the Economic Committee for Health Products, or CEPS) and pharmaceutical companies, starting in the mid-1990s. We contend that state-imposed price controls bring together two types of market governance: a *government of values*, where the aim is to assess medicines according to principles of *social justice* (promoting public health, complying with national health insurance budget requirements, and developing industrial employment), and a *government of conducts*, where the aim is to assess pharmaceuticals in relation to market effectiveness (ensuring that the prices determined will orient pharmaceutical companies and health professionals in the direction of the public interest).

In this logic, we show that the Committee plays two roles. First, it plays a valuative role, as it tries to establish the price of medicines on the basis of an assessment of the therapeutic contribution of the medi-

cine, its public health benefits, and also the prices set on other European markets. Second, it plays a strategic planning role, as it is supposed to manage the overall expenditure on medicines reimbursed by the national health insurance through price-volume agreements and discounts paid by pharmaceutical companies if the target set each year by parliament is exceeded. From this point of view, the Committee does not so much set prices as limit expenditure, which it redistributes among the various companies according to the interest (therapeutic and, to a lesser extent, industrial) of their product range.

Finally, we show that the Committee's policy has not only succeeded in stabilizing the budget devoted by the French parliament to reimbursed medicines, it has also introduced a new price architecture (Chauvin 2011) in which the NHI pays a premium price for a handful of recent medicines with high therapeutic added value and pays at-cost price for a huge mass of old generic medicines or me-too medicines with no or low therapeutic added value. At the same time, the Committee has not succeeded in directly shaping the conduct of physicians who, under the influence of pharmaceutical companies, largely prescribe these new expensive medicines (Nouguez 2017). But it has managed to partially neutralize the effects of these prescribing behaviors on overall medicine expenditure through price reductions on old medicines and generics and through price-volume agreements and discounts paid by companies on new medicines.

From biomedical to social valuation: medicines regulation at the French medicines agency

With Henri Bergeron, Patrick Castel, and Hadrien Coutant, we are currently (from September 2018 to December 2020) carrying out research on the French Medicines Agency (ANSM) (Bergeron, Castel, Coutant, and Nouguez 2019). Based on a rich set of interviews (more than a hundred to date, conducted by us and students under our scientific guidance), some observations of meetings between agency representatives and stakeholders (called "Temporary Specialized Scientific Committees"), and analysis of internal documents, we try to understand the Agency's internal organization, its relationships with stakeholders (other regulatory agencies, government, manufacturers, healthcare professionals, patients), and its strategies and instruments for regulating medicine markets.

Studying the recent history of the ANSM is an opportunity to address market regulation issues (Hauray 2005; Carpenter 2010) and to identify valuation practices in Health and Medicine (Dussauge, Helgesson, and Lee 2015). The history under study may be interpreted as a case of reputation management (Carpenter 2010). Like the US Food and Drug Administration, the French Medicines Agency is embedded in a complex structure of social relationships that strongly impacts its reputation and power and forces it to cautiously manage its audiences. The Agency is trapped between audiences challenging its legitimacy and performance in regulating the market: the Ministry of Health, which is prompt to disavow it under media pressure, and the European Medicines Agency (EMA) with which it shares the power of regulating the market and which may take opposite decisions. But unlike the US FDA, the ANSM since its creation in 1993 has undergone a series of crises that have undermined its reputation and power. The Mediator scandal (2010–12)[5] almost led to the disappearance of the Agency and profoundly disrupted its organization (Ansaloni and Smith 2017). It led to opening up the Agency to its audiences (such as patient associations and medical societies), while establishing a strong barrier against company influence. Moreover, the Agency's management has since 2014 promoted a new regime of regulation that would not only focus on the evaluation of biomedical benefits and risks related to medicines but also take into account social, economic, and political benefits and risks related to the socio-political environment of the Agency.

It is too soon to present definitive results from this research, but we are working around four main assumptions. First, this new valuation regime enriches rather than replaces the health-safety approach, by adding management of social and regulatory risks to the management of biomedical risks. It is thus a way for the Agency to internalize the relationships with the different audiences in its risk assessment and management. Second, it therefore has important consequences for the internal organization of the Agency (leading to the creation or elimination of units within it) and on expert practices within the Agency (leading to new priorities and new assessment criteria). Third, it also plays an important role in shaping the relationships between the Agency and its different audiences (leading to the creation of new interfaces and new modes of association between the Agency and its stakeholders). Fourth, it has an important influence on decisions regarding medicine regulation. A medicine that would not have been authorized from a pure health-safety point of view may be put or stay on the market, because it meets "social needs."

To date, our research has focused on the internal organization of the Agency. We will analyze more closely the effects of this new regulatory regime on the Agency's relationship with its stakeholders and on the

valuation of medicines by following step by step some emblematic cases (levothyroxine, anti-cancer, anti-epileptic, therapeutic cannabis, breast implants). I will also integrate a new research project led by Thibaut Serviant-Fine on the way French public authorities (mainly ANSM and CEPS) are dealing with shortages in anti-cancer medicines and antibiotics.

Conclusion

As a (provisional) conclusion to this (still ongoing) research agenda, I would like to highlight its main contributions to the fields of research in economic sociology mentioned in the introduction.

A first contribution deals with the market organization. In many respects, I have highlighted the complexity of the architecture of the medicines markets, the analysis of which cannot be limited to the strategies of companies or regulators. While there is undoubtedly a process of globalization of production and research and development, medicines markets retain many national peculiarities because they are embedded in healthcare systems whose regulation and organization are still largely national. This has two major consequences for the analysis. First, it is essential to think jointly about the medicines market and the market of health professionals and organizations, because these professionals and organizations are intermediaries in the medicines market and as such contribute to structuring supply and demand, but symmetrically because medicines are a central resource in the positioning of these professionals and organizations vis-à-vis patients and public authorities in the healthcare system. This is illustrated by my research on generics, according to which the statutory competition between brand-name and generic medicines (and their producers) mirrors that between specialist doctors, general practitioners, and pharmacists. Secondly, although the medicines market is not the only one that is subject to strong state regulation, it is undoubtedly one where state control extends to the widest range of dimensions: marketing authorization, technical characteristics of products, property rights, reimbursement, and even prices. This regulation plays a major role in structuring the market, by determining its external (what may or may not be considered a medicine) and internal (what may or may not be considered an equivalent and substitutable medicine) borders but also the conditions and modalities of competition between suppliers and the conditions and modalities of access for patients and health professionals.

As such, it seems to me essential to describe both the formal organization (or structure) of the medicines markets and the organizational work carried out by these different actors. Here again, a whole literature, grouped under the label of "disease mongering" has insisted on the ability of Big Pharma to build and transform markets at the whim of their marketing departments. While it is not at all my intention to deny the financial power of these companies and their great ability to influence regulators, physicians, and patients, I want to emphasize the role of these other actors in structuring medicines markets. If we look at the regulatory agencies, we can only note the inability of the probiotics industry, which is extremely powerful, to influence the position of the EFSA and the European institutions on the regulation of health claims. Similarly, David Carpenter's work on the FDA (2014) underlines the extent to which a unilateral reading of the capture of regulatory authorities by private interests prevents us from grasping the complex and diverse mechanisms of cooperation or confrontation between regulators and the regulated. Much more than total opposition or perfect collaboration between the FDA and the industry, drug regulation in the United States has been based on an alliance built over time between the FDA and some ("reputable," "serious," and "professional") companies around a standard of quality and scientific evidence that excluded other companies (considered "less trustworthy"). If we now turn our attention to healthcare professionals, we can only observe that doctors and pharmacists occupy key positions at all levels of the market, whether as simple prescribing physicians or pharmacists, as university or company researchers in charge of conducting clinical trials and publishing results, or as experts solicited by companies or by regulatory agencies or governments to assess medicines and establish guidelines. Whether we look at regulation or healthcare organizations and professionals, the medicines market does not appear so much as a horizontal architecture bringing supply and demand face to face as a multiscalar and multipolar architecture giving rise to relationships of alliance, competition, and hierarchy between actors with different characteristics and located in different markets and organizations.

A second contribution relates to valuation processes. Like pragmatist works on valuation, I highlight the many uncertainties about the categorization of medicines and people, but more generally about the valuation principles that can be mobilized. Considering whether a product is a medicine or not also means positioning on what disease, health, well-being, or comfort are. Establishing the benefit-risk balance (and not the "ratio," as it is sometimes said) of the medicine relies on evidence from clinical trials but also, as Boris Hauray (2005) has shown, on the legitimacy of the expectations of patients, healthcare professionals, and

manufacturers and on the responsibility of the regulatory agency and these different actors in the circulation of the product on the market. Setting a reimbursement rate or price means valuing not only the therapeutic interest of the medicine but also the capacity and willingness of the NHI to socialize or privatize the expenditure and, finally, the financial support to be provided to an industrial sector, a profession, or a category of patients. In this respect, analyzing the evaluation processes at work on medicines makes it possible to overcome the opposition between the economy and health by introducing a third term: politics. This political dimension of valuation is also to be seen in the use of these operations as an instrument of governance. Valuing a medicine means both assigning values to the product and to the actors who produce, prescribe, or consume it, but it also means organizing a distribution of values (financial, professional, symbolic rewards, etc.) between these actors. And through these operations of attribution and distribution of values, one also designs a possible government of actors' conducts. To take a topical example, the hype surrounding Dr. Raoult's statements and publications on the treatment of Covid-19 with hydroxychloroquine (in combination with an antibiotic) has caused a series of cascading effects on the exponentially growing demand for this medicine (from patients and physicians), on its regulation (the ANSM deciding to reserve the prescription of this product to hospital doctors, provoking the anger of general practitioners who initiated petitions to obtain the right to treat their patients with this medicine like any decent doctor), on its supply (some patients who were taking this treatment for other recognized indications being deprived of it because of shortages), on its production (the government considering rescuing the only French factory producing hydroxychloroquine, which was in bankruptcy), on clinical trials (chloroquine having been included at the last minute in the European clinical trial "Discovery" and some French patients refusing to be in the groups of the trial that would not receive hydroxychloroquine), and so on. By its convulsive dimension, this example is a perfect illustration of the entanglement between market organization and the medicine valuation process. It is also one more case to add to our research agenda in the coming years.

Endnotes

1 Two different words are used for "medicinal product" in English: "drug" is the most common word used in the USA and "medicine" is more frequent in the United Kingdom and Europe. I chose to use "medicine" in this article, as my research takes place in a European context.

2 Jeremy Greene (2014) developed a similar analysis of the introduction of generic drugs in the US thirty years earlier than in France. Despite the differences between the French and American healthcare systems, it is striking to see the many similarities between the generics policies implemented in both countries. See https://www.ema.europa.eu/en/human-regulatory/marketing-authorization/generic-hybrid-medicines.

3 Decriminalization does not challenge the principle of prohibition but is a system that provides use and possession for personal use with soft if no sanction (in particular, deprivation of liberty is excluded *de facto* or *de jure* in such a system).

4 The first list, which contained only generic health claims, was finally adopted in 2012 as an annex to EU Regulation 2012-432.

5 The Mediator is an anorectic (a diet pill) marketed by Servier, a French company, and indicated as adjunctive treatment for type 2 diabetes in overweight patients. It has been massively prescribed off label and has caused the death of hundreds of patients and disabling sequelae in thousands. While this medicine was withdrawn from all European markets in the early 2000s, France waited until 2009 to suspend its marketing authorization. In an inspection report, the Agency was criticized as a "complex, slow, unreactive, fixed organization," as being "structurally and culturally in a conflict of interest situation,", and that had been "inexplicably tolerant of a medicine with no real efficacy" (Ansaloni and Smith 2017). The Agency is being prosecuted as a legal person in proceedings that started in September 2019.

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