ON THE NORMATIVE FOUNDATIONS OF PHARMACEUTICAL REGULATION

ABSTRACT

I argue that behind the 1962 Food and Drug Administration Act we find a combination of two normative principles: a liberal argument for the protection of pharmaceutical markets (in terms of quality control) and a paternalist argument for the protection of pharmaceutical consumers (in terms of drug safety and efficacy). These normative intuitions go hand in hand with the choice of regulatory testing standards: depending on the values the regulator wants to protect, she will avail herself of different testing methods. I explore two potential justifications for regulatory paternalism, in terms of risk aversion and impartiality. I defend our current regulatory arrangement against socialist and libertarian critiques.

1. WHY PHARMACEUTICAL REGULATION?

When philosophers of science started discussing randomized clinical trials (RCTs), now almost twenty years ago, they picked up a thread originally put forward by John Worrall (Worrall, 2002): wrong methodological ideals have undesirable ethical consequences. Adopting RCTs as the gold standard for testing new medical treatments was, for Worrall, epistemically unjustified (Worrall, 2007): there were alternative ways to assess causality that were just as reliable or more. And, moreover, it was morally objectionable to carry out RCTs when other testing methods would provide patients a better chance of receiving the treatment they needed earlier. Here I want to ask the opposite question: what were political values behind the choice of RCTs as a testing standard? And how the methodology of RCTs serves these values? Unlike Worrall and other philosophers, I am not going to discuss the priority of RCTs in evidence-based medicine, but rather the choice of RCTs as our regulatory yardstick for drug safety and efficacy –see, in this same spirit, (Landes, Osimani, & Poellinger, 2017).

The legal foundations of this choice were laid out for the first time in the US, in the 1962 Kefauver-Harris amendment to the Food, Drug and Cosmetics Act (from now on, the 1962 FDA Act). A pharmaceutical company seeking the Food and Drug Administration (FDA) approval for the commercialization of a new treatment should submit to the agency "adequate and well-controlled clinical studies" for evidence of efficacy and safety[1]. The FDA developed this principle in further detail: The "Form FD-

[1] I should warn the reader that I do not presuppose an a priori definition of *safety* and *efficacy*: I rather track the public understanding of both concepts in the United States, namely through regulatory decisions. In the policy-making process, medical reformers operationally defined these concepts in terms of the test

356", published in the *Federal Register* on February 14, 1963, established (Daniel Carpenter & Moore, 2007, 355-356):

> An application may be incomplete or may be refused unless it includes substantial evidence consisting of adequate and well-controlled investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded that the drug will have the effect it purports or is represented to have under the conditions of use prescribed.

The definition of a well-controlled investigation would not be clarified until 1970, when it was formally defined as two well-controlled clinical trials plus one previous or posterior confirmatory trial The standard view among historians and sociologists is that this set of regulations created the modern clinical trial industry. Evidence-based medicine would only arrive three decades later, taking stock of a mass of trials conducted mainly for regulatory purposes.

We therefore need to make some preliminary distinctions: whereas in Evidence Based Medicine (EBM) RCTs should deliver evidence for physicians prescribing treatments, in regulatory RCTs we are merely testing drugs for some predefined levels of safety and efficacy. Whereas these two goals may coincide, they are conceptually different, as EBM supporters often recall: a regulatory trial only shows that a treatment is safe and effective for a particular use, but physicians are often interested in clinical targets not covered in such trials. As we are going to see, pharmaceutical regulation constrains medical prescription, but only to a point: once a drug enters the market, physicians are free to prescribe it independently of the targets covered in the regulatory trials. EBM supporters and regulators may agree on the epistemic superiority of RCTs, but regulators claim this superiority for just one decision (market entrance), whereas EBM supporters ideally want RCT evidence to ground every prescription.

Secondly, philosophers of science have cared about ethical conflicts caused by the trial design, within the realm of research ethics: how shall we protect the participants in a trial? Regulators care instead about protecting patients outside trials:

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a treatment should pass in order to be considered safe and effective. As we will see below, prior to 1962, safety was linked to success in a number of laboratory tests; rom 1962 onwards, safety and efficacy meant success of a treatment in a randomized clinical trial. Of course, we can adopt tighter definitions of both concepts that would question the adequacy of the testing standard: e.g., randomized clinical trials are notoriously underpowered to detect uncommon side effects, which might be sometimes fatal. For the sake of my analysis, vague as they might seem, it is enough with the operational definitions developed by the medical reformers who crafted American pharmaceutical regulation.

namely, the future consumers of experimental drugs. There are potential conflicts (and trade-offs) between these goals, but I will not cover these here (Levine, 1986). My first goal here is making explicit the values presiding over current pharmaceutical regulation, taking the United States (US) as a case study. I am going to argue that the 1962 FDA Act combines two normative principles: a liberal case for the regulatory protection of pharmaceutical markets and a paternalist appraisal of patient safety. The liberal view had been already implemented in the two major regulatory landmarks in US legislation, the FDA Acts of 1906 and 1938. The paternalist view was incorporated in 1962 and has been gradually renegotiated ever since (up to the 21st Century Cures Act[2]). *Of course, these two principles are just idealizations*: in the actual policy-making process, they were combined with each other in various degrees and mixed with many other intuitions. Yet, I think they provide the strongest normative defense of our current regulatory system and allow us to understand the issues at stake in pharmaceutical regulation.

In a nutshell, the liberal argument appeals to the necessity of quality control regulation in order to avoid fraud and litigation. If we want markets to drive the drug development process, a regulatory agency should perform the role of quality safeguard. The paternalist argument goes a step further and presumes that patients should be prevented from accessing some potentially dangerous compounds for their own safety. I am going to discuss the justification of this paternalist stance, distinguishing two different foundations: *risk aversion* and *bias*. The *risk aversion* argument maintains that consumers want a regulatory agency to prevent them from accessing treatments with serious adverse effects for fear of making bad decisions[3]; the *bias* argument, that patients are risk averse (as assumed in the first argument) and, in addition, that they cannot trust physicians to provide an unbiased estimate of the risks of new treatments, given the pervasive conflicts of interest in pharmaceutical markets. Hence, patients defer to an impartial regulator to constrain the prescribing options of physicians. I am

[2] Signed by President Barack Obama on December 13, 2016, the 21st Century Cures Act aims at increasing and speeding the production of new medical treatments. Its Title II Subtitle D ("Modern Trial Design and Evidence Development") invites the FDA to issue guidance that addresses using alternative statistical methods in clinical trials and in the development and review of drugs. The current normative consensus on pharmaceutical regulation discussed in this paper will surely change as a consequence.

[3] What counts as a *serious* adverse effect historically depends on a number of contextual circumstances that I will not discuss here.

going to contend that the risk aversion argument is difficult to sustain *per se*, but that paternalism is still defensible on the grounds of regulatory impartiality.

My second claim is that the regulatory testing methods depend on the values the regulator wants to protect. RCTs are a regulatory yardstick in plain accordance with paternalism: as we will see, it is probably the best tool for conducting *pre-market* tests for pharmaceutical consumers who do not want to bear the risks of experimental treatment. RCTs allow the regulator to test these treatments on a (proportionally, small) sample of patients, before authorizing its use in the general population. Other methods, like observational studies may require a larger number of patients to reach the same conclusions. Under the assumption that pharmaceutical consumers are not risk averse, and leaving other methodological concerns aside, a less paternalist regulator may use these latter methods for either pre-market or post-market testing.

Finally, I am going to defend our current blend of liberal and paternalist views against socialist and a libertarian critiques. The socialist view is that paternalist regulators cannot resist the pressure of markets. The libertarian view is that markets can provide better information about drugs than any paternalist regulator. Both objections show that the choice of our drug testing standards depends not only on the values we are pursuing, but on the social world in which we want those testing standards to work. I will discuss, on the one hand, to what extent pharmaceutical markets are dispensable; and, on the other hand, whether markets can bring us, on its own, a consensual standard on drug safety and efficacy.

2. LIBERAL ARGUMENTS FOR REGULATION

Let me first present what I take to be *the liberal case for regulation*. During the last 150 years, there have been different regulatory regimes for pharmaceutical markets all over the world. From the standpoint of economics, we can explain the emergence of pharmaceutical regulation from the standpoint of the interests of both drug consumers and producers. Drug tests can help in protecting pharmaceutical markets in, at least, two ways. On the one hand, they can check for quality and prevent a particular type of market failure (*adverse selection*). On the other hand, they can check for safety, reducing litigation costs for companies in case of unwanted secondary effects. In both ways, regulatory intervention would foster innovative companies in finding better drugs

for the greater benefit of the consumers. Let us spell this out how in more detail, with some historical illustrations.

Regulation solves a problem pharmaceutical consumers will inevitably face in the market: by their own means they cannot ascertain the quality of a drug, either by simple inspection of their appearance (shape, size, smell…) or by their price. Depending on the circumstances of the patient, the natural rate of variability of their effects (positive or negative) prevents a reliable assessment on the basis of individual experience alone. When buyers or sellers cannot directly determine the quality of a good or service, *adverse selection* (Wilson, 2008) can lead to the elimination of all trade in a market: putting it very simply, if consumers are misled by the existence of cheap (but bad quality) drugs, they will be reluctant to pay the more expensive price requested for good quality compounds and the producers of these latter may end up leaving the market. Regulatory agencies may be potentially justified for the sake of economic efficiency, as a remedy for this type of market failure; they certify a given level of pharmaceutical quality.

We could see adverse selection at work in the US market for "proprietary medicines" at the turn of the 20th century. Pharmaceutical manufacturers sold compounds with undisclosed ingredients and big therapeutic claims, even if most of them were later shown not "to have significant marginal clinical curative power" (D. Carpenter & Sin, 2007, 156)[4]. Given the potential for fraud, consumers and reformers within the US administration were campaigning for an official assessment of the quality of food and, to a lesser extent, drugs[5]. In 1902 the Biologics Control Act, enforced by the Public Health Service of the Treasury Department, regulated the sale of "serums, viruses, toxins and analogous products". It set a minimal degree on control on *biologics*: laboratory experiments on the properties of each compound were the official method employed to verify whether they had any "therapeutic or prophylactic value". The guiding principle was that "evidence of usefulness satisfactory to an impartial investigator must be secured" before recommending a license (McCOY, 1920, 1553). It

[4] The fight against secret remedies in 20th century America is explored in (Young, 1992). The reference work on the evolution of the FDA is (D. P. Carpenter, 2010)

[5] See (Okun, 1986) about the forerunners of the reform and (Anderson, 1958) for an analysis of the campaigns of Harvey Washington Wiley, Chief Chemist in the United States Department of Agriculture and the leading campaigner for the 1906 act.

was easier though to establish lack of utility in a laboratory test (for lack of active principles) than actual effects in clinical trials, for which there was no consensual design. In other words, the 1902 Act could only prevent adverse selection when it was possible to establish that a compound had no substance with known therapeutic properties.

This approach was strengthened four years later, in 1906, when the Pure Food and Drugs Act was passed in Congress. The 1906 Act included provisos about adulterated and misbranded drugs[6]: the Bureau of Chemistry (in the Department of Agriculture) was authorized to seize drugs from the market if the claims featuring in the label (and only there) were untrue. However, the courts would only consider it a fraud if there was evidence that the manufacturer knew these claims to be false. And the testimony of the Bureau's experts about the means to ascertain it was not considered compelling enough to prove whether a manufacturer lied or was simply biased in favor of his product (Marks, 1997, 74-75).

From a legal standpoint, the asymmetry of information about drugs between consumers and producers[7] had already been assumed in American tort law during the 19th century, with a view to protecting consumers from defective pharmaceutical products. Unlike other manufactured goods, purchasers of drugs were entitled to sue the producer in case of tort, instead of the immediate seller. The assumption was that neither the retailer nor the consumer could know the risks or benefits of a drug, but the manufacturer should anticipate them. At the same time, strict liability in tort was imposed on manufacturers: an injured plaintiff did not need to prove intent, negligence or fault, as long as it could be proven that the drug caused the injury. American courts have traditionally favored the customary medical use of drugs in cases of tort claims. Hence, for pharmaceutical manufacturers innovation was potentially costly. Having an independent third party assessment of the safety of drugs, could protect the industry from litigation and foster drug development.

[6] The debate on the 1906 Act is analyzed in (Young, 1989). See also (Marks, 1997, 73-74).

[7] Adverse selection presupposes an asymmetry of information: variations in the quality of individual goods can be observed by only one side of the market. In principle, the manufacturer knows better the ingredients of a compound and their properties than any buyer.

This is a potential (*post hoc*) interpretation of the incorporation of safety tests in the 1938 Federal Food, Drug, and Cosmetic Act (Vardon, 2003)[8]. Drug producers were now required to demonstrate that their compounds were "safe for use under the conditions prescribed, recommended or suggested in the proposed labelling thereof", before it was commercially distributed. The FDA created a system of expert consultants to decide on the therapeutic merit of the submitted drugs, under the utilitarian principle that a drug was safe if its "proposed use would benefit patients more than it harmed them" (Marks, 1997, 72). Again, the applications were screened through laboratory analysis and animal experimentation. If there were still doubts about the toxicity of the drug, clinical evidence was obtained from well controlled trials conducted by a group of trusted experts. Despite an increased emphasis on the need for a sufficient number of cases, if the evidence was not conclusive the last word was for the most experienced expert in each case. This is how the principle of pre-market review established in the 1938 Act was implemented. In order to avoid liability claims, the industry agreed with the FDA that it would not be compelled to provide directions for consumers' use in the labels of its products.

[8] The passage of the 1938 Act is discussed in (Jackson, 1970) and (D. P. Carpenter, 2010, 73-117).

Hence, the first normative pillar of pharmaceutical regulation is based on a conditional: if we want pharmaceutical markets to drive the process of drug development and commercialization, there are economic arguments for regulatory quality controls or safety checks. The antecedent of the conditional is what makes this argument for regulation *liberal*: as we will see below, not everybody would want markets to guide pharmaceutical research. But, to the extent that markets are actually playing that role, there are arguments for having it regulated for its own protection[9].

3. REGULATORY PATERNALISM AND RISK AVERSION

Let me now present the paternalist argument for pharmaceutical regulation: regulatory paternalism occurs when the treatments available for physicians to prescribe are constrained not just in terms of quality, as in the previous argument, but also in terms of safety and efficacy. Physicians (and patients) are denied access to certain treatments because they are not considered safe or effective enough, independently of the stakeholders' views. This form of regulatory paternalism, I will argue, underlies the adoption of RCTs as the testing in the 1962 FDA Act. But, as we are going to see, regulatory paternalism was never explicitly justified: it was tacitly grounded on the collective risk aversion to adverse effects triggered by the Thalidomide tragedy. However, on its own, risk aversion is not a solid foundation for regulatory paternalism: we are going to see as well how it has been gradually eroded over the last four decades.

According to (Marks, 1997, 155), the road to the 1962 FDA Act started in the 1950s. A minority of therapeutic reformers fought a "shadow war" marshaling arguments to persuade "a largely silent medical community" of the necessity of adopting RCTs to evaluate the therapeutic merit of drugs. The 1950s saw a boom in industrial drug production (some were *wonder drugs*, e.g. antibiotics, but many were just combinations of already available compounds) and, simultaneously, in

[9] Julian Reiss (personal communication) objects that my articulation of the liberal argument presupposes that regulation protects pharmaceutical markets better against adverse selection than more market-oriented solutions, such as expert advice on drugs or privately sponsored assessments. As a matter of principle, we cannot rule out these solutions, but it is worth considering why in our past history none of them has ever worked, despite their apparent simplicity. For instance, it is worth considering why the American Medical Association (AMA) dismantled its pioneering Seal of Acceptance program precisely at a time (the 1950s) in which companies were bringing to the market many great drugs. According to Podolsky (2015, 31-33) the contributing causes were the combined pressure of the own AMA marketing branch, the lack of resources for assessing every drug submitted and litigation against AMA for failed assessments. Precisely the problems we have been discussing regarding the FDA. Which institutional setup would allow a private assessment system to overcome these obstacles?

pharmaceutical advertising that caused much confusion among practitioners about the therapeutic merit of each product (Marks, 1997; Podolsky, 2015). In this context the idea of testing drugs not just for safety but for *efficacy* arose, and it quickly reached the FDA.

No precise definition of safety or efficacy was given, but it was generally linked with a demand for more strict tests, often expressed in public by FDA officers[10]. Safety had been shown so far by all sorts of laboratory tests and trials. Now, safety had to be observed in RCTs statistically powered to detect a given clinical effects: if these latter could be achieved without serious adverse effects, the new treatment could be considered safe. It was this severe approach to testing which allowed the FDA officer in charge of the Thalidomide application, Frances Kelsey, to resist pressure from Merrell, the American manufacturer, to approve the drug for marketing in the U.S. (D. P. Carpenter, 2010, 217-297). For Kelsey, the evidence about safety submitted by Merrell was insufficient, methodologically defective and at odds with the literature and the expert opinion on the drug. Hence, she resisted approval, gradually increasing the burden of proof, at a point in which Thalidomide was liberally used outside the United States. What initially seemed unjustified stubbornness on the part of Kelsey came later to define the FDA standard regulatory outlook, once the reports of Thalidomide-caused phocomelia reached the US. Defenders of a more severe pharmaceutical regulation in Congress found in the Thalidomide scandal the occasion they needed to pass what would become the 1962 Kefauver-Harris amendment to the Food, Drug and Cosmetics Act. It required from the applicant "adequate and well-controlled clinical studies" for evidence of efficacy and safety. Without them, new treatments would not be allowed in the market.

The physician's decision as to how much a patient could benefit from a given drug was now externally constrained by these new testing standards: whereas in the pre-1962 conception of safety, there was room for clinical judgment in the assessment of drugs, after 1962 prescription was only possible if there was a previous RCT certifying

[10] "As of the summer of 1969, the Administration had not yet codified its interpretation of the Food, Drug and Cosmetic Act's requirement for "substantial evidence" of effectiveness. The main criteria for effectiveness had instead been elaborated informally, often in speeches by Joseph Sadusk, Frances Kelsey, and Commissioner James Goddard in the early and mid-1960s. […]The May 1970 rules defined "well controlled studies" in flexible but rigorous terms, explicitly excluding "isolated case reports, random experience, and reports lacking the details which permit scientific evaluation." (D. P. Carpenter, 2010, 354)

together safety and efficacy. If the FDA considered a compound unsafe or ineffective, it would not be available for prescription, even if the physician and the patient were willing to take their risks. Regulation goes here well beyond the liberal protection of pharmaceutical markets: it adopts a *strong* paternalistic stance regarding pharmaceutical consumers.[11] Of course, medical prescription is, by default, paternalist: the patient is usually not in a position to properly decide on her own treatments. The benevolent supervision of a physician (under the Hippocratic Oath) has been traditionally considered a good enough basis for prescription. The 1962 FDA Act went far beyond and *constrained the number of therapeutic choices available to the physician in terms of efficacy, without any consent from the patient and for the sake of her own health*.

This is what I call *strong regulatory paternalism* and it has not been subjected to much philosophical discussion, because Kelsey's argument by example has been considered almost self-evident by pharmaceutical consumers. Kelsey's paternalistic caution went perhaps beyond the spirit of the 1938 Act, but she clearly avoided adverse effects that no pregnant mother would have desired for her baby. As Dan Carpenter puts it, throughout the following decades "the legacy of thalidomide was a powerful one, and every time a new drug safety issue arose, the memory of the drug and its disfigured victims was evoked" (D. P. Carpenter, 2010, 300-1). So far, the US public has not massively complained about an excess of regulatory safety, but sometimes the opposite[12].

The collective fear of adverse effects has tacitly sustained the regulatory paternalism of the FDA. But, as such, there is nothing intrinsically moral about this fear. As a vocal minority of libertarian critics soon claimed, not every patient wants the same levels of regulatory protection in every circumstance (D. P. Carpenter, 2010, 300-345). For instance, Louis Lasagna, a John Hopkins pharmacologist who had been an early FDA advocate, became a staunch critic in the 1970s. Together with William Wardell, Lasagna argued that the testing standards of the FDA were sacrificing the welfare of

[11] As one of my reviewers observed, it would be possible to appeal to the liberal argument for introducing the 1962 FDA Act rather than (or in addition to) the paternalistic arguments. Indeed, the Act could have been justified in terms of the superior protection it offered against adverse selection. But the actual arguments of the Kefauver-Harris hinged on consumer protection understood in a paternalistic manner. The FDA could have tested the drugs and deliver the assessment to the consumers for them to make the decision about taking potentially risky compounds. But this was a route never taken.

[12] The construction of the FDA regulatory reputation went far beyond Thalidomide though: see the fifth chapter of (D. P. Carpenter, 2010) for a full account.

today's patients for the protection of future patients (Wardell & Lasagna, 1975). Unlike the tests required in the 1938 Act, RCTs are long and costly experiments that delay the introduction of new treatments in the market. The 1962 FDA Act denied access to experimental treatments to patients who may benefit from them and are willing to bear the risks. For Wardell and Lasagna this was immoral. They advocated instead a return to a weak form of medical paternalism about treatments, such that "if a respectable minority of professional opinion believes in the utility of a drug, then it ought to be available for use by those who believe in it" (Wardell & Lasagna, 1975, 38).

In other words, if physicians and patients were willing to bear the risks of a new treatment, when no conclusive evidence was available about its effects, no regulatory authority should prevent them from trying it. Wardell and Lasagna supported their arguments on a libertarian appraisal of the Declaration of Helsinki on human experimentation (article 37th), revised in the same year they published their book to affirm that "concern for the interests of the subject must always prevail over the interests of science and society."

4. RCTS AND THE JUSTIFICATION OF REGULATORY PATERNALISM

The 1962 FDA Act combined then the liberal argument for market protection already implemented in 1906 and 1938 with a paternalist argument for patient protection. Whereas the liberal argument requires a weak concept of safety (based on quality control), the paternalist argument strengthens safety subordinating it to efficacy, as shown in RCTs[13]. I am going to contend now that there is indeed a tight link going through *methodology* between the normative principles behind pharmaceutical regulation and th drug testing standards adopted. Take *sample size*, for instance: if we assume pharmaceutical consumers to be risk averse, paternalist regulators will want testing methods that minimize the number of patients exposed to the risks of experimental treatments. If we assume instead that pharmaceutical consumers are willing to take their risks, leaving other considerations aside, less paternalist regulators can try methods that require bigger numbers of patients.

[13] The view that the degree of safety of a treatment must be viewed in light of its therapeutic value emerged at the FDA during the 1950s. So far, the FDA had acted as a liberal regulator that checked for quality and safety, but left to the prescribing physician the assessment of a treatment's therapeutic value. The emerging view wanted to conduct a centralized assessment using RCTs as a standard (D. P. Carpenter, 2010,150-ff). The justification for this was a superior degree of protection for the patient, provided by a paternalistic regulator.

In the regulatory development of the 1962 FDA Act, the safety and efficacy of a drug was operationally defined in terms of success in a RCT. The virtue of RCTs in protecting consumers lies in their purported internal validity in grasping the causal effects on a treatment. In a clinical trial it is possible to control for many more factors than, e.g., in an observational study: in principle, this should allow trialists to reach their conclusions with fewer subjects and less biases[14]. In other words, testing a treatment on a comparatively small sample of consumers will allow the regulator to protect a much bigger population. This is precisely what a paternalist regulator wants: since the population of patients is assumed to be risk averse, *RCTs minimize the number of patients who need to be exposed to experimental treatments in order to make a decision.

If the assumption is removed and a big enough number of patients are willing to bear the risks, the range of methodological options available for the regulator grows. In a large observational study, the variance of the estimator decreases. Its reliability, as compared to RCTs, will depend on how well the observational design controls for biases[15]. This is the methodological rational of the regulatory approach advocated by Wardell and Lasagna, for whom the FDA should return to its 1938 functions and just check for drug quality. Physicians should test new drugs with patients who, in their judgment, may benefit from the drug and consent to the risks. With an adequate reporting system, the FDA could detect early serious adverse effects and withdraw compounds, if necessary.

It is crucial to bear in mind this connection between political values and testing methods, because, I contend, the changes in the latter signal implicit shifts in the former. As a matter of fact, the FDA was not completely insensitive to the anti-paternalist argument of its libertarian critics and developed a compassionate use policy, giving access to experimental treatments on a case-by-case basis. But the revolt of AIDS patients against the AZT trials in the late 1980s forced the FDA to articulate a more systematic advanced access policy(Epstein, 1996). Organized around the networks created in the 1970s gay movement, Act Up gathered AIDS patients in active opposition to regulatory paternalism, demanding access to new drugs in the name of their individual rights to bear the risks (Epstein, 1996, 222). As Larry Kramer, one of their

[14] See (Senn, 2008) for a discussion in terms of the bias-variance trade-off.

[15] Philosophers of science often argue that the ability of RCTs to control for biases is overestimated (see, e.g., (Borgerson, 2009), I take sides here with (Senn, 2008), who claims the opposite.

leaders, put it, “AIDS sufferers, who have nothing to lose, are more than willing to be guinea pigs" (*ibid*.).

In response the FDA articulated its accelerated approval program, in which new treatments were examined in shorter trials, using surrogate endpoints as predictors of clinical efficacy. For instance, treating a disease like cancer until its actual remission may take years, delaying the regulatory decision accordingly. RCTs can be designed targeting instead a biological marker that obtains earlier after treatment and nonetheless reliably predicts the treatment actual endpoint (survival or death) (Teira, 2017). This methodological shift shows, in my view, a compromise between regulatory paternalism and individual rights, in which the former is relaxed *a bit*. Using a surrogate outcome instead of the actual treatment endpoint decreases the levels of efficacy for pharmaceutical consumers: RCTs in which we observe a prediction of clinical efficacy will fail more often than trials in which the actual clinical efficacy is observed. Therefore, the regulator drawing on the former may go wrong more often in her gatekeeping decisions, exposing future patients to bigger risks.

5. REGULATORY PATERNALISM AND IMPARTIALITY

Let me take stock of the argument so far: I have argued that the 1962 FDA Act combines liberal and paternalist ingredients about drug safety and efficacy. These normative intuitions go hand in hand with the testing methods of the regulatory agency. The paternalism of the 1962 FDA Act is implicitly justified in terms of the risk aversion of pharmaceutical consumers. But I think that this justification is far from satisfactory. On the one hand, as a matter of principle, not every patient has the same level of risk aversion in every circumstance, so there is no *a priori* consensual level of regulatory protection. On the other hand, throughout the last few decades, the FDA has *de facto* accepted that there is room for different levels of consumer protection, gradually modifiying its testing methods in a way that relaxes the 1962 Act paternalism.

Why not jumping ahead in this slippery slope and let every patient choose what risks to bear if in need of an experimental treatment? I am going to present now an alternative defense of regulatory paternalism, based on the following intuition: in order to take one’s chances with an experimental treatment, we want impartial information about the risks we are bearing. If there is uncertainty, we want a fair presentation of our chances. Pharmaceutical markets on its own cannot reliably provide this impartial estimate, since the commercial interest at stake systematically bias the information

presented. Hence, it is rational for pharmaceutical consumers to defer on a regulator for the pre-market assessment of new drugs, for lack of a better evidential source. Let me spell this out.

The paternalist and anti-paternalist arguments presented above have a common presupposition: in the own words of Wardell and Lasagna, "any system of weighing evidence will ultimately stand or fall on the honesty and wisdom of the individuals making the judgment" (Wardell & Lasagna, 1975, 38). A regulator deciding on the safety and efficacy of a drug on the basis of RCTs and a physician prescribing an untested drug to a patient should do it upon their best clinical judgment. However, historians have shown that the 1962 FDA Act emerged in a context of growing mistrust in the marketplace, where clinical judgment was under a constant threat of distortion caused by pharmaceutical advertisement to physicians. The same Louis Lasagna claimed only a decade earlier against the "sleazy advertising" practices of the pharmaceutical industry, trying to persuade physicians with "badly scissored quotes", "pharmaceutical numbers racket", "detail men" visits and so forth (Lasagna, 1959, 460-461)[17]. Physicians and patients, on their own, cannot discern clinical facts from marketing claims.

There is here is a potential justification for regulatory paternalism in terms of a Ulysses contract (Spellecy, 2003): given the pervasive biases of physicians and patients in judging over treatments, and in particular their defective appraisal of the risks they entail, it is rational for them to transfer to a qualified third party (the pharmaceutical regulator) the power to test every new treatment before they can have access to it. Furthermore, if patients cannot trust physicians to prescribe new treatments upon this evidence, it is rational for them to have an impartial regulator to constrain the prescribing options of physicians according to a pre-established level of safety[18].

Whereas the previous argument was about the willingness of patients to bear the risks of new treatments, this second case is about their chances to obtain unbiased information about those risks from the prescribing physician. And, indeed, behind the

[17] For an analysis of how the fight against pharmaceutical marketing drove the adoption of RCTs in the United States see, most recently, (Podolsky, 2015).

[18] Julian Reiss rightly objects again that a regulator may not be the only alternative and that less interventionist alternatives are conceivable. However, we have had experience of some of these approaches under our current regulatory regime and their degree of success is sobering: see, for instance, (Jain, 2007)

1962 Act we find a growing concern about the partiality of physicians, exposed as they were to all sorts of misleading evidence originating in the marketing departments of the industry[19]. In this regard, the adoption of RCTs as a regulatory yardstick was often defended in terms of the warrants of impartiality they incorporated: methodological devices such as randomization, blinding, and a pre-established interpretation rule (*p*-values) prevented the stakeholders' interests from interfering on the trial result (D. Teira, 2013). Assuming this protection was effective, RCTs would provide unbiased evidence regarding the safety and efficacy of new treatments, at least as compared with the uncontrolled clinical judgment of physicians exposed to pharmaceutical advertising. Strong regulatory paternalism would be just the constriction of the prescribing choices of physicians in terms of an impartial assessment of risks.

For this defense of paternalism to hold, we need the pharmaceutical regulator to be actually impartial. After all, if there was no such impartiality, why deferring on a paternalist agency that is no less biased than your physician of choice? Despite the frequent critics against the FDA for being accommodating with the demands of the industry, I concur with Dan Carpenter that so far it has reasonably accomplished its regulatory mission with reasonable fairness[20]. However, no methodology or deliberative procedure provides a definite warrant of impartiality. Bennett Holman aptly describes this process as an ongoing *arms race* between the industry and the regulator in which commercial interests try to by-pass every debiasing method implemented (Holman, 2015). Ultimately, any regulator can be *captured*. Regulatory capture occurs when, given a definition of the public interest that the agency should protect (e.g. guaranteeing that only safe and effective drugs get access to markets), there is evidence of the

[19] "To get an approximate idea of the current situation in all specialties, the author reviewed the summaries of original investigations which appeared in the *1959-60 Year Book of Drug Therapy*. Out of 394 summaries which gave adequate information about the plan of the study, 225 (57 per cent) related to reports without any explicit comparison with the results of another treatment in similar patients. Every section of the *Year Book* contained reports which ignored the hard fact of unpredictability and simply described the course followed by patients while they were being given a drug. All of this evidence suggests that a great part of the so-called clinical evaluations of new drugs is unscientific, lacks adequate provisions to eliminate bias, and cannot be objectively judged." (Sheps, 1961, 651)

[20] In my view –and I follow Carpenter, once more, here–, both regulatory RCTs and the FDA itself have been reasonably effective so far at fulfilling their main mission: keeping out of the market unsafe compounds. The main evidence for this claim is the number of treatments withdrawn from the market for serious adverse effects (Carpenter , Zucker , & Avorn 2008). That is, the sort of Thalidomide scenarios that the 1962 FDA Act was aimed at preventing. In this regard, if either the evidence or the committees had been biased, the harm has not big enough to threaten the regulatory authority of the FDA.

industry acting on the agency and evidence about regulatory actions shifting away from the public interest toward industry interest (D. P. Carpenter, 2014).

Capture is a threat for *both* the liberal and the paternalist arguments for pharmaceutical regulation. Capture can happen both to institutions checking for quality (liberal safety) or for efficacy (paternalist safety). There are two opposite answers to this threat. On the one hand, there is the socialist approach: if ultimately no regulator can stand the pressure of pharmaceutical markets, let us make these latter shrink as much as we can. On the other hand, there is the libertarian approach: since no regulator is better at estimating risks than the prescribing physician, let markets handle drug assessment. I will examine each of these two arguments in the following sections in order to support further my defense of the *status quo*. I will contend first, against the socialist objection, that we need the levels of innovation brought about by pharmaceutical markets. If we foster competition in these latter, not only there will be more innovation, but the risk of capture will also diminish. Therefore, there is still a chance for an impartial regulatory agency such as the FDA. I will then argue, against the libertarian, that on their own, markets are unlikely to yield the impartial assessment of new drugs that pharmaceutical consumers, as of today, seem to require.

6. A SOCIALIST VIEW OF PHARMACEUTICAL REGULATION

According to the most critical voices about the pharmaceutical industry, pharmaceutical capitalism, as we know it, has already captured the FDA and the only possible correction is to minimize the role of markets in the development and distribution of drugs. The Danish physician Peter Gøtzsche exemplifies this position (Gøtzsche, 2013): being one of the leading experts in the meta-statistical analysis of RCT biases and a former pharmaceutical insider, Gøtzsche's arguments provide qualified evidence for the widespread view that Big Pharma are intrinsically bad.

For Gøtzsche, agencies like the FDA cannot properly fulfil their mission of testing for safety: according to his estimates, the incorrect use of drugs kills about 100.000 patients per year in the US alone, making it the fourth aggregate cause of death (after heart conditions, cancer and chronic lower respiratory diseases). For these estimates, Gøtzsche relies partly on actual death reports, but also on meta-analyses: if a treatment causes *x* deaths for every 100 patients treated, it is enough to multiply per the number of patients receiving the treatment in the country to make up a figure. In his view, the failure of the FDA at gatekeeping for safety is plain *corrosive* capture by the

pharmaceutical industry: although the legal mandate is there, the FDA is impotent to enforce it. On the one hand, because it relies on industry sponsored trials which are designed in the best interest of the sponsor[21]. Its outcomes are presented in a completely unmanageable format in which actual effects are easy to hide. On the other hand, the FDA officers discourage scientists at the agency to pursue evidence of harm, accept fraudulent data and even react slowly to the evidence of lethal harm.

Leaving aside his estimates about the deathly effects of drugs and sticking to FDA own statistics, the numbers are equally appalling: "No less than 51% of drugs have label changes because of major safety issues discovered after marketing; 20% of drugs get new black box warnings; and more than 1 in 20 are withdrawn from the market" (Gøtzsche, 2013). It could actually be worse, since the FDA simply neglects the problem of polypharmacy (what happens when different treatments are administered simultaneously), and we have not enough evidence about the safety of combined treatments that have been approved separately.

In Gøtzsche's view, the ultimate cause of this sorry situation is pharmaceutical capitalism: "Pharmaceutical research is perverted by market incentives", he claims. "In 2012, the top 50 companies sold $610 billion in human prescription pharmaceuticals. I have little doubt that we could easily save 95% of this, which are annual savings of $580 billion" (Gøtzsche, 2013). Again, if we take these figures at face value, pharmaceutical markets would seem almost dispensable. And this is indeed Gotzche's proposed reform:

- State-owned drug companies and need-driven research
- Publicly conducted trials and publicly available data
- Tougher approval criteria and better labelling
- No need for drug marketing

Summing up, if capitalism is distorting the impartial judgment of regulatory agencies of safety, let us simply minimize the role of pharmaceutical markets in both drug development and commercialization. For the sake of the argument, let us assume

[21] For instance, in trials with subjective outcomes, it has been shown that using an assessor who is not blind to the treatments received by patients overestimates the treatment effect. Yet, blinding is not implemented in a systematic manner: see (Hróbjartsson et al., 2012).

that Gøtzsche's estimates are correct: the question is whether nationalizing the pharmaceutical industry would indeed provide us with safer and more effective drugs. Pharmaceutical regulation is, indeed, not an end in itself: it is only meaningful when the industry is capable of producing innovative drugs. In this regard, it is worth recalling an old libertarian point: the USSR, where state-owned companies developed drugs based on public needs, was never pharmaceutically innovative (Jack & Mason, 1987). Moreover, we owe to capitalist incentives the development of the first generation of truly effective compounds (e.g, aspirin, anesthesia), despite the medical objections against pharmaceutical markets. According to Joseph Gabriel (Gabriel, 2014), in the 19th century US, the medical profession considered "ethical" those drug manufacturers that somehow tested their products before commercialization, disclosed the composition of their remedies, abided by purity standards set by the US pharmacopeia, and cultivated their reputation for quality rather than trademarks and advertising, without any patent protection. However, the professional consensus among physicians on these "ethical" standards collapsed by the last quarter of the 19th century. In part this was driven by the emergence of companies with strong foundations in chemistry (rather than botanical medicine) and the new "synthetic" compounds. These medicines were clearly more effective than the traditional pharmacopeia, but were nonetheless, "unethically" patented and advertised[22].

In other words, state-owned companies can fail to deliver innovation (as in the USSR), whereas for-profit firms, despite their "unethical" standards, can innovate on their own initiative. As we saw before, regulation, in its liberal version, aims to protect innovative pharmaceutical companies. The question is: *what is there in markets that ultimately causes the capture of the regulator*, flooding markets with *me-too* drugs and unsafe compounds. This is a question I cannot obviously settle here, but there are good conceptual grounds to defend that the problem is not pharmaceutical capitalism. Let us borrow here an argument by Michele Boldrin and David K. Levine, two economists for whom the *monopolies* created by patents on drugs would explain both lack of pharmaceutical innovation and overinvestment in advertising. In this view, *market competition* would provide the best remedy (Boldrin & Levine, 2008).

[22] In the last quarter of the 19th century, a majority of the medical profession thought unethical to patent drugs: not disclosing their composition and exploiting them commercially for private benefit (Gabriel, 2014).

In a very simple textbook scenario (ignoring competitors and imitators), there is a crucial difference between the incentives of an inventor to innovate in a competitive and a monopolistic regime. Under a number of very simple assumptions about demand and production, it can be shown that in a competitive industry, the inventor's only incentives to innovate are the profits that any cost-reducing invention would yield. When such inventions are protected by patents, other firms cannot use it to lower their costs and compete on prices. Hence, for the monopolistic inventor there is no need to innovate further to obtain the same profit. This profit becomes a *rent*.

According to Boldrin and Levine, patents provide such *rents* to the pharmaceutical industry. Hence, the industry would lack incentives to compete on cost-cutting innovations: *it is actually cheaper to invest in advertising*. Technically this is known as *non-price competition*. For instance, me-too drugs just change the characteristics of a compound without actual innovation and invest instead in advertising the changes as if they were substantial. Only 238 out of the 1035 drugs approved by the FDA between 1989 and 2000 contained new active principles and were given priority ratings on the basis of their clinical performance (Boldrin & Levine, 2008, 231).

Summing up, there are conceptual grounds to think that the dysfunctions in pharmaceutical markets leading to regulatory capture can be alleviated if we foster, rather than minimize, competition. Ultimately, this could be achieved with the abolition of pharmaceutical patents, for which Boldrin and Levine have produced powerful theoretical arguments. Without patents, pharmaceutical companies would be forced to invest in developing new treatments and conduct trials that showed actual efficacy. For competitive companies, there would be no need of capturing the regulator, since competition brings out quality drugs. The regulator would protect these companies from rogue competitors producing fake drugs (as in the liberal argument).

Of course, this stylized case is far from conclusive, but it shows, at least, that there is no conceptual contradiction between the two normative principles that guide pharmaceutical regulation. Liberal markets do not necessarily lead to the capture of regulatory agencies. As a matter of fact, Boldrin and Levine's argument about the power of markets is so powerful that it might actually pose the opposite question: if market competition alone can deliver actual innovation, why would we need a regulator at all?

7. A LIBERTARIAN VIEW OF PHARMACEUTICAL REGULATION

Julian Reiss has precisely made this radically libertarian case, although also on epistemic grounds: if we question the assumption that RCTs provide the gold standard for testing treatments, regulation becomes a matter of expert judgment (Reiss, forthcoming). And, for Reiss, there are no good reasons to believe that the FDA's experts are any better than those of industry. Fostering market competition would provide incentives for the industry to develop treatments of credible quality. As to the risks entailed by these treatments, the only responsibility of the industry would be to convey them properly to the consumers, so that, in case of adverse effects, tort law would help to adjudicate guilt in court, if necessary.

We might wonder though what a proper signal for credible quality is. In this regard, Reiss goes for *contextualism*. There are different methods for grasping causal effects and each one of them may yield valid conclusions depending on the circumstances. Hence, each pharmaceutical consumer should receive enough education to discern for herself about the quality of the available evidence. Regulatory agencies would be, in this view, dispensable. Yet, I think that both the liberal and the paternalist arguments presented above are still defensible, because there is something that competitive markets, on their own, are not probably going to bring about: evidence based on shared standards of proof.

For a start, no amount of statistical education for consumers is going to make up for the lack of evidence. A serious problem we currently have with industry-sponsored RCTs is that these tests do not address the clinical questions that might be most relevant for actual prescription, but rather those that either would earn the drugs regulatory approval or give them an edge on me-too competitors (Goldacre, 2013). It is, perhaps, conceivable that market competition could align the interests of patients, physicians and pharmaceutical producers in such a way that one single test would be good enough for them all. But the economics of science shows that for one such consensus to exist the conflicting parties should agree first on a set of rules defining what counts as a good test (Zamora, 2002). In particular, what makes the test impartial regarding the different interest at stake (David Teira, 2013). Without this constitutional agreement about methods, pharmaceutical markets will remain in an epistemic "state of nature" with self-interested agents contesting each other's claims about the efficacy of drugs whenever it does not fit their particular interests.

In actual practice, can we expect market competition to bring us somewhat close to this methodological consensus? There is evidence to think that dispensing with patents, good as it may be for innovation, may not help us to reach one such agreement: as Jeremy Greene has recently shown, in the US market for generics trials are still controversial. On the one hand, this is because it is not so simple to agree on the concept of bioequivalence between drugs with the same active principle:

> [T]wo pills with the same amount of the same therapeutic ingredient can cause different effects on the human body if they dissolve at different times in the stomach, if their active principles appear at different rates in the bloodstream, or if their binders, fillers, dyes, and shellac coatings influence their action in the human body in different ways (Greene, 2014, 93-94)

On the other hand, assessing the comparative effectiveness of drugs is equally open to interpretation. Citing Greene again, we need to agree on these three core questions:

> First, how could one measure the comparative effectiveness of drugs for a given therapeutic class? Second, how could one evaluate the comparative safety of these drugs? Third, when two or more drugs were found to have similar safety and efficacy in a general population, were there any subgroups for whom that similarity did not apply? (Greene, 2014, 238)

So far, we have not seen a consensual response emerge in generic markets. As a matter of fact, we see a growing number of public institutions dedicated to therapeutic comparisons (e.g, in the UK, the National Institute for Health and Clinical and Excellence) precisely in order to provide this kind of evidence as a sort of *public good*.

Without an agreement on standards of proof, there are reasons to expect that markets alone will not correct any asymmetry of information about drugs. We may expect adverse selection to kick in massively – as it happens today in pharmaceutical marketplaces where regulation is not enforced, as is the case of Nigeria (Peterson)[23].

[23] Kristin Peterson's etnography shows how the lack of enforcement of the pharmaceutical regulation in Nigeria (based on a British system) led to the proliferation of all sort of fake and defective drugs in West Africa. For Peterson, this should be mostly blamed on the neoliberal policies implemented in Nigeria. For our purposes, her case study illustrates instead to what extent minimally regulated markets (without checks for safety and efficacy) can generate a credible signalling system about drug quality. Of course, this particular case does not prove that such signalling systems may not emerge. It just illustrates once

And we should not expect litigation alone to correct it. E.g., if a patient sues a company for incorrect advertising of the risks a treatment involves: on the basis of which evidence is the court to adjudicate the claim? Given the costs of running a clinical trial, in its most modest estimates, the financial asymmetry between companies and consumers will just reinforce the asymmetry of information[24]. Therefore the liberal argument for regulation would still hold: if we want markets to guide the drug development process, there should be a regulatory check for quality.

And the same logic supports the paternalist case for regulation: without a shared standard of proof, patients should blindly trust the clinical judgment of their physicians to choose treatments[25]. This sort of trust is not epistemically indefensible as such, but it presupposes no conflict of interest on the part of the prescribing physician. Can we expect pure market competition to increase or minimize these conflicts? Again, this will depend on our expectations on pharmaceutical advertisement. Can we expect market competition to make it more faithful to the actual properties of treatments (according to a particular yardstick of efficacy)? Will it contain the sort of mistrust in the advertising marketplace that brought about the FDA in the 1950s? My own guess is based on the fact that we have been so far unable to reach a consensus on what is rational to prescribe neither for patented drugs (see, e.g., the exemplary discussion of antibiotics in (Podolsky, 2015)) nor for generics (Greene, 2014). For patients, it may be rational to have a social convention on what counts as safe and effective for most and constrain the physicians' choices. This is the sort of Ulysses contract enforced today by the FDA, a basic form of paternalism with a number of established exceptions[26].

8. CONCLUDING REMARKS

Let me summarize my arguments to close. I have argued that behind the 1962 FDA Act we find a combination of two normative principles: a liberal argument for the

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more that, to the extent of my knowledge, we have not seen these systems emerge in our recent pharmaceutical history.

[24] Even if countries like the UK there are public subsidies for hiring private forensic experts, the costs of RCTs are in a totally different order of magnitude –in the latest guideline "unusually large" forensic costs are those over £5000

[25] On the epistemic problem of choosing expert advice when statistical evidence is involved, see (González De Prado Salas & Teira, 2015).

[26] Apart from the accelerated approval track discussed above, the FDA also fast tracks breakthrough therapies, improving on current standards of treatment, and grants priority reviews, which gives approval on an application within six months.

protection of pharmaceutical markets (in terms of quality control) and a paternalist argument for the protection of pharmaceutical consumers (in terms of drug safety and efficacy). These normative intuitions go hand in hand with the choice of regulatory testing standards: depending on the values the regulator wants to protect, she will avail herself of different testing methods.

The risk aversion of pharmaceutical consumers provided the original justification of the paternalism of the 1962 FDA Act. RCTs should screen off unsafe and useless compounds in order to prevent Thalidomide-like tragedies. However, as libertarian critics soon denounced, not every patient requires the same levels of consumer protection in every circumstance. I have developed a different justification for regulatory paternalism in terms of the impartiality of the drug assessment. If a patient wants to take her chances with an experimental treatment, she needs a fair estimation of the risks involved. Against the libertarians, I have argued that markets alone are not likely to provide this impartial assessment. But we need pharmaceutical markets, nonetheless, against the socialist critique, and if we foster proper competition in these markets, we will see that regulatory agencies like the FDA will thrive for everybody's benefit. As Dan Carpenter has often argued, the FDA is quite unique as a government agency, both in terms of its mission and the reputation it has achieved (D. P. Carpenter, 2010). I think the current arrangement deserves continuity since we do not have solid grounds to think that the alternatives will fare better.

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