A DEFENCE OF PHARMACEUTICAL PATERNALISM

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Abstract

Pharmaceutical paternalism is the normative stance upheld by pharmaceutical regulatory agencies like the US Food and Drug Administration. These agencies prevent patients from accessing treatments declared safe and ineffective for the patient's good without their consent. Libertarian critics of the FDA have shown a number of significant flaws in regulatory paternalism. Against these objections, I will argue that, in order to make an informed decision about treatments, a libertarian patient should request full disclosure of the uncertainty about an experimental treatment. But pharmaceutical markets, on their own, are not a reliable source of information about such uncertainty. And companies have the power to capture any independent expert who may assess it. Therefore, the libertarian is better off deferring on an independent regulatory body the assessment of the pharmaceutical risks, constraining access to treatments until tested.

Keywords: paternalism, libertarianism, pharmaceutical regulation, FDA, asymmetric information.

Most readers of this journal probably live under a regime of pharmaceutical paternalism. They cannot buy the medical treatments they want, but only those that have been approved for medical use by a regulatory agency. The pharmaceutical regulator paternalistically decides whether a treatment is safe and effective enough for patients to have. This has not always been the case. Until the early 20th century most medical treatments, true and fake, could be freely accessed in the pharmaceutical marketplace. With the chemical revolution that brought about modern drugs and the emergence of the first health insurance systems, the State gradually regulated pharmaceutical market and restricted access to treatments.

In the United States, whose Food and Drug Administration (FDA) set the paradigm for regulatory agencies over the world, a 1905 Act established external certification of the composition of drugs. In 1938, only drugs that the FDA tested for safety could access pharmaceutical markets. Safety was strengthened with efficacy in the 1962 Act that created the current standard for regulatory paternalism: only those drugs that succeeded in a demanding experiment (the Randomized Controlled Trial [RCT]) were authorized for commercial use.

Unlike medical paternalism (patients can only access medical treatments under prescription), pharmaceutical paternalism has received comparatively little philosophical attention –until Jessica Flanigan's recent monograph.[1] With the growth of regulation, pharmaceutical libertarianism was gradually articulated in the United States as a critique of the FDA and a vindication of patients' rights to decide, on their own, about the risks they are willing to take with their treatments. Like other forms of libertarianism this was a fringe position until the rise of organized patient activism in the 1980s. For three

decades now, patients have demanded quicker access to experimental treatments, pushing the FDA to arrange special testing schemes or compassionate use programs to meet their demands. The passage of the 21st Century Cures Act in 2016, with a whole new set of directives for quicker drug testing, is the latest move in softening the original paternalistic stance of the FDA.

The gradual relaxation of pharmaceutical paternalism invites normative reflection on its limits. Should our societies reconsider the trade-off between regulatory oversight and patients' autonomy? In order to contribute to this debate, I will try first to make explicit what I take to be the normative foundations of the FDA regulatory arrangement. I will argue that these foundations combine a liberal and a paternalistic leg. The liberal case for regulation wants to prevent the consequences of asymmetries of information in pharmaceutical markets. Unless a regulator certifies what counts as a legitimate drug, it is too easy to scam patients selling them fake treatments. The paternalist argument for regulation seems to be based on collective risk aversion: in order to prevent pharmaceutical tragedies caused by defective drugs, let us have a regulatory agency with gatekeeping power to screen off dangerous compounds from the market.

Libertarians and patient activists have mostly targeted the paternalistic leg of the argument, showing its shaky grounds. Risk aversion is an individual characteristic very sensitive to time and context, so it does not provide a broad consensual ground for paternalistic restrictions. I think that this objection is solid. Yet I think it is possible to construct an alternative defence of pharmaceutical paternalism drawing on the consequences of the asymmetries of information addressed in the liberal case for regulation. My argument takes the form of the classical Ulysses contract[2]. In order to make an informed decision about risks, I contend that a libertarian patient should request full disclosure of the uncertainty about an experimental treatment. But pharmaceutical

markets, on their own, are not a reliable source of information about such uncertainty. And companies have the power to capture any independent expert who may assess it. Therefore, the libertarian is better off deferring on an independent regulatory body the assessment of the pharmaceutical risks before making any decision.

Against my Ulysses contract I will consider two recent arguments by libertarian authors. Flanigan has argued that establishing the safety of a drug is a value judgment since safety ultimately depends on patients' values on which he is the best judge. Julian Reiss has argued that there is no single method that allows us to establish, once and for all, when a drug is safe. Market competition can deliver that information more efficiently. I will present a rejoinder against two objections, and, in the final section, consider the future of pharmaceutical paternalism.

The liberal argument for regulation

The liberal argument for pharmaceutical regulation hinges on preventing what economists call *adverse selection.*[3] Pharmaceutical consumers cannot discern, by their own means, whether anything sold as a drug is an actual medical treatment. A pill may look, smell and taste like a drug, while it is, in fact, a placebo. Moreover, an individual trying the drug cannot expect to infer its actual effects on other patients: the biological variability of human organisms will bring about differences between the patients' reactions to any treatment, be it real or a placebo. Under these circumstances, there are big incentives for companies to produce fake treatments: they are cheaper to develop than real drugs and, therefore, the prices will beat any competition. Therefore, we may expect that rogue companies will drive legitimate manufacturers out of pharmaceutical markets. A regulatory intervention may be thus justified in order to protect the development of real treatments via market incentives. A regulatory agency can test new drugs for certain

properties characterizing authentic treatments, so that consumers can choose among them without being deceived by defective compounds.

There is, indeed, evidence that lack of properly enforced regulation triggers pharmaceutical adverse selection. In a pioneering study sponsored by the World Health Organization[4], it was estimated that 1 in 10 medical products in developing countries is substandard or falsified. On the one hand, there is high demand for good quality drugs but the supply is either low or unaffordable. On the other hand, governance is poor and there is limited technical capacity to supervise the quality of the drugs available in the market. The most expensive component of a medicine is usually the active ingredient. Reducing the amount in the dose invariably increases the profit margins and it is less likely to be detected, provided it has some effects –even if it does not cure the patient. Falsified packaging and seals are easy to obtain. And provided there are high enough sales, even cheap medicines provide an opportunity for counterfeiters, since their benefit depends on the profit margins. Once these fake drugs reach the markets, adverse selection starts: in some African countries, pharmacists declare that "in order to compete with the illegal street markets and hawkers of medicines they are compelled to source their products from the cheapest but not necessarily the safest suppliers in order to keep their business afloat".[5] The WHO is laudably coordinating efforts to alert consumers about fake treatments, but the benefits are so high that fraudsters can afford to invest in counterfeiting authentication devices and still sell cheap.

The liberal argument for pharmaceutical regulation hinges then on a conditional: if you want markets to drive the development and distribution of medical treatments, it is necessary to regulate, differentiating between legitimate and illegitimate drugs, in order to protect markets against adverse selection

[6].

The paternalist argument

Current regulatory regimes across the world have followed the lead of the 1962 FDA Act, by which the agency should test new compounds for safety and efficacy, paternalistically preventing patients from accessing those treatments that fail the test[7]. Safety and efficacy were pragmatically defined in terms of the type of test used to establish them. The pharmacologists at the FDA successfully promoted the adoption of the RCT as the regulatory standard. RCTs are comparative experiments in which the new treatment is tested against the standard therapy or a placebo according to a statistical protocol that would allow to assess the significance of any difference in the outcomes. Two positive RCTs provide a regulatory proof about a treatment being safe and effective.

The political driver of the 1962 FDA Act was the Thalidomide tragedy, a sedative that, if administered during pregnancy, caused severe malformations in babies (phocomelia). Francis Kelsey, a pharmacologist at the FDA, delayed the introduction of Thalidomide in the US alarmed by reports about its adverse effects in Europe. She resisted the pressure of the manufacturing company and denied access to the drug to the physicians and patients who requested it. Her approach exemplifies the sort of paternalism institutionalized in the 1962 Act. From then on, the FDA has constrained the freedom of physicians and patients to prescribe or consume drugs, without the consent of neither physicians nor patients, for the sake of their good health.

Technically, this is a strong form of pharmaceutical paternalism that goes well beyond the liberal argument. In the latter, it is a priori enough to differentiate between good and bad treatments (however good and bad are defined), leaving to consumers the decision to use them. The paternalist argument deprives consumers of this option in a way that, so far, has been widely accepted by the concerned publics. Historians and political scientists of the FDA, our best known case study, have shown how this acceptance has

often been driven by pharmaceutical tragedies. The gate-keeping power of the FDA was acquired in the 1938 FDA Act, after the scandal of the 100 deaths caused by the antibacterial Elixir Sulphanilamide –improperly prepared with a toxic solvent. FDA officers successfully campaigned then for a pre-market approval system as the best defence of public safety.[8]

We may wonder why the call for public safety is best served with a paternalist control of market choices. In the debate leading to the approval of the 1938 and 1962 there was no systematic argument justifying this option: apparently, the public just wanted to avoid pharmaceutical tragedies and pre-market screening seemed a good enough strategy for the US Congress. The lack of an explicit consensual justification is somewhat surprising, since, as Carpenter observes, other than drugs, no other credence goods (whose quality cannot be ascertained even after purchase and consumption) are regulated in this paternalistic fashion.[9]

Yet, the evidence available suggests that the politics of drug regulation is comparatively less ideological or partisan than in other fields: the consensus on the necessity of a gatekeeping agency is broad.[10] We may conjecture that there may be sufficiently widespread normative intuitions favouring paternalism. In my view, there are two main sources for these paternalistic intuitions. On the one hand, there seems to be some sort of *collective risk aversion* regarding pharmaceutical treatments. Untested treatments may have, with an unknown probability, positive and negative outcomes in the form of a cure or adverse effects. Most pharmaceutical consumers seem to be risk averse in the sense of preferring a (tested) treatment with a sure outcome to an (untested) treatment with potential gains and losses.

Of course, risk aversion neither involves nor justifies paternalism protection for risk prone individuals. Yet, short of a more explicit argument, it may explain why the

regulatory paternalism of the FDA has been broadly accepted among US citizens.[11] At least, as we are going to see next, risk aversion helps us to understand the objections against regulatory paternalism raised in the US through the last four decades. In a nutshell: there is a minority of patients, small as it may be, with different preferences about risk whose demands have weakened the FDA regulatory paternalism, making explicit the necessity of a proper justification.

The arguments against regulatory paternalism

According to Daniel Carpenter, self-medication flourished with patent medicines in the *ante bellum* US, until the passage of the 1938 FDA Act.[12] It combined reliance in consumer autonomy and disdain for State interventions. However, we only find the first conceptual articulation of this stance in the libertarian opposition to the 1962 FDA Act. The arguments of Louis Lasagna and William Wardell provide a prominent example.[13] In a book published by the American Enterprise Institute, a conservative think tank, Lasagna and Wardell argued against the perverse consequences of strong regulatory paternalism. In their view, RCTs delay for years the access to experimental treatment, from which some patients could already benefit, for the sake of preserving the safety of future pharmaceutical consumers. The welfare of today's and tomorrow's patients seemed not equally worthy. This trade-off was unacceptable for Lasagna and Wardell because there are always risks to treatments and there is no failsafe test, not even RCTs. Ultimately, if a physician thinks that a patient may benefit from an experimental drug and the patient is properly informed and willing to take the risks, no regulatory agency should prevent her from accessing the treatment.

For Lasagna and Wardell, strong regulatory paternalism should be replaced for traditional medical paternalism. The latter is not as daring as straightforward self-medication –which was more difficult to sustain at a time in which treatments had become

increasingly complex. Yet, Lasagna and Wardell granted patients the right to decide on their own risks, challenging the idea of public safety presented in the previous section. Accidental harms are acceptable provided that the concerned parties agree open about the risks and liabilities involved in taking experimental treatments. In recent years, the strong regulatory paternalism of the FDA has mellowed in response to this sort of concerns. E.g., Right to Try Laws allowing patients with a diagnosed terminal condition to access experimental drugs for which there are no positive regulatory RCTs, just with their informed consent.[14]

The question is why making regulatory exceptions in order to give quicker access to some patients, while other patients are denied this privilege. Being terminally ill does not mean that there is nothing to lose. Critics of the Right to Try Laws have argued, correctly in my view, that experimental treatments can make things not just better, but also worse for terminally ill patients. Untested therapies can add suffering via adverse effects or simply accelerate death. There are still risks to take and assessing them is as much a personal decision for the terminally ill as for any other patient. But, if this is the case, it is difficult to resist the conclusion that every patient should be given a chance to try experimental treatments, provided that she alone bears the consequences.

To sum up, if public safety is understood in terms of risk aversion, the objections of both patients' activists and libertarians are convincing, in my view. Risk aversion is an individual feature that is sensitive both to context and time.[15] The same individual will be more or less risk-prone depending on the situation. Why would it make sense to constrain her treatment choices once and for all, independently of the circumstances? Would it not be preferable to spell out the risk for every particular treatment choice, so that the patient has enough information to decide on her own?

A new argument for regulatory paternalism

I want to offer now an argument for strong regulatory paternalism that, I hope, will persuade some libertarians. In a nutshell it goes as follows. I grant that, ultimately, a patient should have the right to decide on the risks she wants to take. Yet, for this decision to be properly informed, I expect that libertarian patients will want to have the full available evidence on the risks she is taking. The uncertainty in the decision should be genuine in the sense that none of the concerned stakeholders (healthcare providers, manufacturers, insurance companies) can exploit such uncertainty for its own benefit, at the patient's expenses. I contend that we cannot expect unregulated markets alone to provide this sort of information and, therefore, it is rational for the libertarian patient to accept a strong regulatory body on the basis of a Ulysses contract. Given the asymmetries of information about treatments, if a patient can be exploited for the benefit of a third party, it is better to defer on an impartial regulator the decision of which treatments should be prescribed. Let me spell out the argument in this section and discuss two potential objections in the next one.

As for the first premise, leaving patients the last decision on the risks they want to take, let us grant it for the sake of the argument, since the aim is to persuade a libertarian for whom this will be a given. The key point is the second premise: in order to make an informed decision about risks, I contend that a libertarian should request full disclosure of the uncertainty about an experimental treatment. That is, what are the potential outcomes and how likely they are.

Generally speaking, for a libertarian, being able to make mistakes through having the right to make one's own choices leads in the long run to more self-reliant, competent, and independent individuals[16]. In the case of medical treatments, the challenge is whether patients can actually learn from their unsupervised market choices about the safety and efficacy of the treatments they take. The asymmetry of information about treatments

discussed in the liberal argument for regulation reappears here. The inter-individual variability of reactions to medical treatments makes impossible individual learning about the whole range of treatment effects. These effects only become apparent in aggregate data from large samples of patients. Neither individual patients nor individual physicians in their daily practice can grasp them.

Yet, a libertarian may not want to learn, but just rather exert her right to self-medicate, bearing the consequences. I assume that this libertarian patient will want to choose without being manipulated: the treatment seller should not hide any relevant information for her choice. The patient will suffer the consequences of taking the treatment, in the first place, so for her consent to be properly informed, all the uncertainty about the treatment effects should be laid out. However, the available evidence about unsupervised pharmaceutical markets suggests that such full disclosure rarely occurs. In my view, this is a straightforward consequence of adverse selection. The asymmetry of information allows inferior quality compounds to proliferate and manipulate customers into buying them with all sort of deceptive claims. Here is where a libertarian may want a Ulysses contract –a term coined by coined by Rebecca Dresser and defended by Ryan Spellecy: given the impossibility for patients to ascertain the real uncertainty about treatment effects, it is rational for them to transfer to a regulatory agency the power to test every new treatment before they can have access to it.[17]

Such a contract will be more or less appealing depending on the estimated uncertainty of new treatments. E.g., in a world in which all fake treatments were sugar pills, trying them without any supervision would not have harmful consequences in most cases. In my view, the only realistic guess on the risks a patient would face in a libertarian pharmaceutical market relies on our current regulatory experience. Let us see what the

risks are under the strongly paternalistic supervision of the FDA in order to guess how challenging the risks in a libertarian scenario could be.

As of today, no other testing method has been implemented more systematically by the FDA than RCTs. Regulatory RCTs provide estimates about whether a new treatment will yield, on average, a given therapeutic outcome. Regulatory failure occurs when an approved drug causes cause serious adverse effects or death that should have been detected by the RCTs. In these cases, the FDA withdraws the drug from the markets. Judged by the number of withdrawals, the levels of regulatory failure have been historically low: less than 2% of new drug approvals by the FDA between 1950 and 2011 were withdrawn.[18]

Nonetheless, the number of adverse effects reported is low, but not negligible in absolute figures. The World Health Organization runs since 1968 an international database that records adverse effect reactions registered in drug monitoring centres from dozens of countries. Between 2000 and 2005, for instance, the United States contributed 953.919 adverse effects (or 537.6 reports per million inhabitants).[19] As a matter of fact, many drugs remain in the market with more or less serious adverse effects detected after approval, since the FDA considers that some patients may still benefit from them. These adverse effects are then recorded in the product label, by way of warning and disclaimer. According to some prominent critics, many of these drugs should be equally recalled and they only remain in the market for the financial interest of the pharmaceutical industry. For instance, according to Peter Gøtzsche, by 2007, 20 million consumers had taken Zyprexa, an anti-psychotic drug for which the FDA had issued a warning already in 2003. Meta-analyses would have shown that for every 100 patients treated in a trial, there was a death on the drug. Therefore, taking into account the total number of consumers,

200.000 patients may have died for a drug that, in Gøtzsche's view, should have been recalled[20].

In other words, under the strong paternalistic regime of the 1962 FDA Act, there is uncertainty to medical treatments: there is a low, but non negligible, probability of adverse effects or death. In addition, there is not complete symmetry of information between the pharmaceutical industry and the prescribing physicians. These latter may certainly count on, at least, the two positive RCTs required for market approval. But the industry often knows more thanks to unpublished trials. According to a recent study, an astonishing 45,2% of the outcomes of the approximately 25.927 RCTs registered at ClinicalTrials.gov by major trial sponsors have not been published.[21] There have been prominent campaigns advocating for a legal mandate to register all the conducted trials and release the raw outcomes (e.g., AllTrials.net), but the level of disclosure, under our current regulatory regime, is only partial.

So, in a full libertarian scenario in which pharmaceutical companies compete directly for the patient's treatment choice (with or without a physician's supervision) we may expect the uncertainty to increase significantly for, at least, the first cohorts of patients that try a new drug, until the aggregated data reveal the true treatment effects. This is a learning process that nowadays takes between 5 and 10 years through an optimized RCT protocol. At the same time, in a libertarian scenario we may reasonably expect that pharmaceutical companies will release even more selectively the information they have gathered about their products. All this, assuming, of course, that the pressure of adverse selection in a completely unregulated market did not make it just crumble.

Under these circumstances, I think that a Ulysses contract is appealing for the libertarian patient. An impartial regulatory agency should test the treatments before they are released to the market, so that the most complete information about their risks is

available for the patient before she makes her final decision about which drugs to take. This Ulysses contract does not support the strong regulatory paternalism of the 1962 FDA Act or the 21st Century Cures Act, but we shall discuss the differences in the conclusion. Let us now consider two potential objections to the argument from a libertarian perspective: either safety is a value judgment on which the only competent expert is the patient or there is no best scientific method better than the market to ascertain it.

Declaring a treatment safe is a value judgment

In a recent monograph, Jessica Flanigan has provided the most systematic philosophical defence so far of pharmaceutical libertarianism.[22] Flanigan grounds the right to self-medication on a Millian epistemic principle: "no one but a person himself can judge whether a risk is worth taking because each person understands and cares about his own interests more than anyone else."[23] For Flanigan, health is a non-instrumental part of a person's overall well-being, and there is nobody is in a better position to judge how a treatment may impinge on a patient's well-being than the patient himself. Even if the patient's judgement is not reflective enough in the eyes of a third party, it does not diminish the patient superior grasp of his wellbeing.

According to Flanigan, the right to self-medicate and the doctrine of informed consent are closely linked[24]: if the patients have the capacity to consent to an approved medical treatment, under our current regulatory regime, they should be equally capable to assess the risks on experimental treatments. The weaknesses and biases in the patients 'judgment are equally interfering in both cases. And, crucially, the FDA approval makes no substantive difference between drugs. For Flanigan, "drug safety is a normative judgment that requires knowledge about how the risks and side effects of a drug fit into a patient's life as a whole."[25] In other words, a drug is not safe because it tests positive at

two regulatory RCTs, because in these experiments risks are assessed independently of the patients' particular interests and values.

This conception of drug safety openly challenges the mission of the FDA (and, *a fortiori*, my own Ulysses contract defence of regulatory agencies). For considering the approval of an experimental drug, the 1962 FDA Act required the submission of "adequate and well-controlled investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved". For Flanigan, the only competent expert would be the patient, since the expertise of physicians, valuable as it is, does not reach the interests and preferences of patients. Of course, Flanigan acknowledges the risks in an untested drug, but if the patient is properly informed about these risks, his consent is enough to validate the decision about taking the treatment.[26]

How to inform the patient properly? Flanigan defends an institutional certification system, in which a public agency tests the treatments already sold in the market and assesses their effects without gatekeeping powers.[27] Patients could then use the lack of certification as an indicator of the unknown unknowns about a treatment. If the manufacturer misled the consumers with deceptive claims, later proved false by the certification authorities, patients should just sue them.

Flanigan provides no details about how to implement this certification system, but there is an a priori difference between her approach and my Ulysses contract: the latter involves to restrict access to new treatments until they have been properly certified, whereas for Flanigan access should be granted as soon as the compound is ready to be marketed. For risk-averse patients there may be no practical difference between both arrangements, since they will probably wait until the certification is awarded. But those patients who really want to take their chances will be deprived of access until certification in my approach, whereas they will have no restriction in Flanigan's. Against my Ulysses

contract argument, the response of these libertarian patients would be something like: "Lack of certification is a powerful enough warning about the risks I am taking. If the manufacturer tries to deceive me with the treatment claims, I can just sue him later on".

My rejoinder is that asymmetries of information do not disappear by declaring safety a normative concept. Asymmetries just reappear in court when a plaintiff has to gather the necessary facts to support his complaint. For most patients, litigation against pharmaceutical companies, particularly on defective drug design or testing, is simply not a viable means for redress. In order to make my case, I will now use some empirical evidence about the current regulatory scenario in the US as a benchmark to assess the plausibility of Flanigan's proposal. I will briefly examine the entanglement between pharmaceutical regulation and tort law.[28]

It is a dual system: even if the FDA declares a product safe, a patient may sue the manufacturer for drug injuries on three different accounts: negligence, strict liability in tort and breach of contract. Negligence may occur in designing, testing, manufacturing or labelling a drug. Even if there is no negligence, if a product defect causes an injury, the plaintiff may sue the manufacturer for strict liability. Yet, unlike other consumer goods, for the US legislator, drugs have "unavoidable risks", and strict liability does not apply if "the product is properly prepared and accompanied by proper directions and warning". Hence, the plaintiff should argue that the risks were avoidable for either improper design, manufacturing or labelling. Breach of contract is just the breach of warranties and rarely applies to drugs.

The vast majority of drug lawsuits have been for defective manufacturing or failure to warn (i.e., update the drug label after the initial release), either under negligence or strict liability in tort.[29] Given the tight regulatory supervision of the drug development process, it is difficult to sue manufacturers for negligence or avoidable risks in the design

and test of a drug.[30] Besides, pharmaceutical companies invest millions in the drug development process and finding alternative evidence to show that negligence in this process caused patient harms is difficult in most cases.[31] Moreover, even when this evidence is available, both judges and juries of lay citizens (with, on average, secondary education) are usually overflown by the sheer amount of scientific data from different disciplines required to settle the case.[32] This makes the outcome of litigation unpredictable and, therefore, deterring for most plaintiffs.

Let us consider, as an illustration, the class actions against the analgesic Vioxx, usually considered a success story about patients obtaining redress thanks to evidence documenting the mortal side effects of the drug. Indeed, Merck, the manufacturing company, reached a settlement compensating patients with $4.85 billion. Yet, Merck's initial strategy was precisely not to settle, winning in 11 of the first 16 trials completed. Merck's line of defence hinged, on the one hand, on FDA approval (against strict liability) as and, on the other hand, on lack of evidence about Vioxx being the proximate cause of death.[33] Jurors occasionally declared Merck guilty, perhaps moved by the claims of alleged corporate dishonesty (withholding information about cardiac risks). But after the first sixteen trials, it became clear for the plaintiffs that it was too difficult to show that Vioxx had actually caused the patients' death against Merck's legal and scientific firepower. The company then offered $4.85 billion settlement just to avoid further legal costs. The settlement imposed tight conditions on the plaintiffs –e.g. they had to accept it without a clear estimate of the compensation they would individually receive.[34] If the number of plaintiffs had been smaller (around 50.000), Merck could have chosen to defeat them in court. When the evidence of harm is not sustained by big numbers, litigation may simply fail and impose serious costs for plaintiffs.[35] In other words, even under our

current regulatory regime, asymmetries of information between patients and manufacturers are difficult to revert.

Ideally, Flanigan's certification system would level this asymmetry of information. Harmed patients will be able to litigate on the basis of an independent assessment of treatments. But the devil is in the details and Flanigan provides very few. A certification system that simply provides ex-post a test of safety and efficacy does not eliminate the asymmetry of information regarding the development of a treatment. It just opposes two different tests about safety and efficacy (the industry and the certification authority's), leaving to patients the burden of the proof about failures in design and manufacture, making the outcome of litigation even more unpredictable than in the current regulatory regime. This strengthens my Ulysses contract argument. Having full regulatory oversight on every compound until its market release makes litigation accessible for patients.

Of course, a principled libertarian patient may just claim that, independently of any further legal action, she is entitled to take her risks and lack of certification is all the necessary warning. Ulysses arguments will have no traction on a Ulysses that just wants to listen to the sirens unbounded. But, leaving aside any further principled discussion, it would be relevant to know how many daredevils would not be covered either by the exceptions in our current regime or my own alternative arrangement (post-testing access)[36]. Given the potential losses for everybody else (the liberal argument), would this minority support a broad enough consensus to change the current system?

The market is enough to discriminate the better treatments

Let us now consider the more radical approach of Julian Reiss.[37] Whereas Flanigan did not challenge the standardized assessment of risks conducted by regulatory

agencies, Reiss questions the epistemic superiority of RCTs. In a traditional libertarian vein, Reiss argues instead that market competition would deliver a better assessment of the actual risks of medical treatments. Here is the argument. First, for Reiss RCTs are not the gold standard for testing treatments. RCTs are methods for causal inferences with a number of limitations that have been extensively discussed among philosophers of science: for instance, how to extrapolate the conclusions of the drug test from the experimental sample to the actual population on which it will be used. There are multiple methods for causal inference about the effects of a treatment and any of them might be the best tool depending on the circumstances of the case under analysis. Choosing which one should be used is a matter of expert judgment, for which there is no algorithm.

If this is the case, Reiss' second step is to claim that a priori there is no reason to presume that FDA experts are better than industry experts in assessing the consequences of a treatment. Both have biases: those at the industry care about their sponsor (the more products in the market, the better), those at regulatory agencies care about the institutional reputation (the less regulatory mistakes, the better. How shall we choose? According to Reiss, and this is the third step, real market competition will provide incentives for the industry to develop treatments of credible quality. As of today, pharmaceutical markets are not competitive, since companies exploit the monopolies created by drug patents, without real incentives to innovate. Fostering market competition will yield, for Reiss, better treatments. If manufacturers reliably provide the information about their effects gathered by their experts, and consumers receive a minimum of education about how to interpret it, patients will learn on their own which treatments are better. In case of injury or fraud, tort law provides, for Reiss, enough protection for consumers.

Unlike Flanigan, Reiss does not elaborate on the normative premises of his libertarian approach, but rather focus on a matter of epistemic principle: under which

conditions could markets deliver a better safety assessment than regulatory agencies? If there was a positive answer, this would clearly undermine, if not defeat, my Ulysses contract: libertarian patients may expect to revert the asymmetries of information thanks to market dynamics, at least in the long run.

Part of the arguments I have presented so far provide a response. As to the first step, the performance of regulatory RCTs has been good enough, but perhaps other methods may improve it. This remains to be seen and empirical evidence about it is necessary to accept Reiss' claim. I equally doubt that tort law, on its own will protect pharmaceutical consumers, given the huge evidentiary burden for the plaintiff gathering the facts and for the jury and judge who should assess them. Standard economic models provide also reasons to be sceptical about the virtues of litigation: when the stakes are high, as is the case of health, the amount of compensation claims may simply incentivize companies to distort the liability system (e.g., declaring bankruptcy).[38]

Yet, the objection remains that, under certain circumstances, market competition may overcome the asymmetries of information between manufacturers and pharmaceutical consumers, so a full libertarian may be in principle possible. I am going to argue that we have no a priori reason to expect markets to provide that necessary information. More precisely, for each treatment, there would be two unknown factors: on the one hand, the outcome variable that will signal treatment success (e.g., a physiological indicator); on the other hand, the best method to estimate the true value of the outcome variable. In order to make a proper choice, patients should know which success variable to look for in a treatment and which method is the best to estimate it.

Under the 1962 FDA Act, there is no rule as to the former, but RCTs provide a default estimation method. The debates on which is the better outcome variable are endless, because often there is more than one and any choice may be defended on a

number of grounds. For instance, the acceptance of surrogate outcomes (early indicators predicting treatment success) was originally justified in order to accommodate the patients' demands for quicker trials, but has been later on criticized as a self-serving tool for industry interests: it is, generally, easier to get market approval with a carefully chosen surrogate outcome than with a final treatment endpoint (e.g., death of the patient). So under the current regime, the situation is far from perfect. How could we assess the chances of achieving via market competition a better arrangement?

The economics of science studies how market competition between scientists may yield scientific outcomes.[39] The identification of the two unknown factors about medical treatments discussed above has been generally appraised as a *constitutional* problem in science: before scientists can compete, they need to agree on the rules of the competition in order to declare a winner. Otherwise, the best strategy for a self-interested scientists would be to contest everybody else's claims of success in order to maximize his own chances of a win. In the economics of science we find discussions about the general properties that variables and methods should have in order to reach a constitutional consensus (e.g., impartiality regarding the competing theories).[40] But there is no general proof that scientists in an unregulated competition may reach an agreement on epistemically relevant variables and methods. Furthermore, even if an external third party (a patient) sets the relevant target variable to be measured, there is no way for her to check whether a given scientific agreement on methods provides the best estimate. This is just another asymmetry of information known as the principal agent problem, for which again, there is no general solution yet.[41]

So, in the best possible scenario for Reiss' argument, we would not have proof yet that market competition, under ideal circumstances, can neither identify the relevant unknown factors (outcome and method) nor overcome the asymmetries of information

between pharmaceutical companies and patients. This strengthens my Ulysses contract argument for the libertarian patient.

Concluding remarks

In this paper, I have contributed a reconstruction of the normative foundations of regulatory agencies such as the FDA, defending that they combine a liberal case for the protection of pharmaceutical markets with a paternalistic stance justified in the terms of the risk aversion of pharmaceutical consumers. This latter argument has been correctly criticized, in my view, by both libertarians and patient activists, because risk aversion is a highly variable individual characteristic. I have proposed instead a Ulysses contract defence of pharmaceutical paternalism: in order to make an informed decision about risks, I contend that a libertarian patient should request full disclosure of the uncertainty about an experimental treatment. An independent regulatory agency, I contend, provides the most reliable source for such an assessment.

An interesting consequence of my argument is that it would nonetheless transform the current paternalistic regime. Once the regulator delivers the risk assessment, the libertarian patients should be free to access those experimental drugs that had failed the test, provided that an informed consent form with all the necessary liability provisos had been signed. So far patient activists demand access to yet untested treatments, so perhaps only a small minority would be interested in these failed compounds, but I think it would be worth granting them access.

The signal it would send to patients is that pharmaceutical regulation is concerned with the protection of both pharmaceutical markets and consumers against asymmetries of information, setting the proper grounds for informed consent. Pharmaceutical tragedies occur when improperly tested treatments were sold through chemists to the unadvised

patient. An individual application procedure for dangerous drugs that have proven so in

a test will avoid such tragedies: if a disgrace occurs it will be as voluntary and informed

as any other medical decision in our society can be.

[1] Jessica Flanigan, *Pharmaceutical Freedom: Why Patients Have a Right to Self Medicate* (Oxford University Press, 2017).

[2] Following the example of Ulysses (Odysseus), who agreed with his crew that they would tie him up to the mast so he could listen the sirens sing, ignoring all his requests to set him free.

[3] Charles Wilson, 'Adverse Selection', in Steven N. Durlauf and Lawrence E. Blume (eds.) *The New Palgrave Dictionary of Economics* (Basingstoke: Palgrave Macmillan, 2008).

[4] Worl Health Organization, *Global Surveillance and Monitoring System for substandard and falsified medical products* (Geneva: World Health Organization, 2017).

[5] Worl Health Organization, op.cit., p. 23.

[6] We should bear in mind that it is, indeed, a conditional. Many pharmaceutical critics challenge precisely the antecedent: the markets as such are responsible for the troubles of pharmaceutical consumers and regulation is just a poor remedy for them –*e.g.*, Peter C. Gøtzsche, *Deadly Medicines and Organised Crime: How Big Pharma Has Corrupted Healthcare* (London: Radcliffe Publishing, 2013). This is why I deem *liberal* this leg of the argument for pharmaceutical regulation.

[7] I owe my understanding of the history and institutional role of the FDA to Daniel P. Carpenter, *Reputation and Power* (Princeton: Princeton University Press, 2010).

[8] Carpenter 2010, op. cit., p. 96.

[9] Daniel Carpenter, 'Is Health Politics Different?', *Annual Review of Political Science,* 15 (2012): 287-311.

[10] Carpenter 2012, op. cit.

[11] Carpenter 2010, op. cit.

[12] Carpenter 2010, op. cit., pp. 75-80.

[13] William M. Wardell, and Louis Lasagna, *Regulation and Drug Development* (Washington: American Enterprise Institute for Public Policy Research, 1975). See Carpenter 2010, op. cit., pp. 300-345.

[14] D. Carrieri, F. A. Peccatori, and G. Boniolo, 'The Ethical Plausibility of the 'Right to Try' Laws', *Critical Reviews in Oncology/Hematology,* 122 (2018): 64-71.

[15] Daniel Kahneman, and Richard H. Thaler, 'Anomalies: Utility Maximization and Experienced Utility', *Journal of Economic Perspectives,* 20 (2006): 221-34.

[16] I take these two claims from Gary Becker's post: "Libertarian paternalism: a critique" (January 14th, 2007): http://www.becker-posner-blog.com/2007/01/libertarian-paternalism-a-critique--becker.html (visited on December 22nd, 2019)

[17] See Ryan Spellecy, 'Reviving Ulysses Contracts', *Kennedy Institute of Ethics Journal,* 13 (2003): 373-92. As a reviewer rightly observes, my argument does not amount to a justification of the FDA, since I do not discuss under which circumstances a regulatory agency would correctly perform the mission assigned in the Ulysses contract.

[18] I. J. Onakpoya, C. J. Heneghan, and J. K. Aronson, 'Post-Marketing Withdrawal of 462 Medicinal Products Because of Adverse Drug Reactions: A Systematic Review of the World Literature', *BMC Medicine,* 14 (2016): 10.

[19] A. Bate, M. Lindquist, and I.R. Edwards, 'The Application of Knowledge Discovery in Databases to Post-Marketing Drug Safety: Example of the Who Database', *Fundamental & Clinical Pharmacology,* 22 (2008): 127-40.

[20] Gøtzsche, op. cit.

[21] A. Powell-Smith, and B. Goldacre, 'The Trialstracker: Automated Ongoing Monitoring of Failure to Share Clinical Trial Results by All Major Companies and Research Institutions', *F1000Research,* 5 (2016): 2629.

[22] Flanigan, op. cit.

[23] Flanigan, op. cit., p. 6.

[24] Flanigan, op. cit., p. 12.

[25] Flanigan, op. cit., p. 10.

[26] (Flanigan, 2017, p. 24)

[27] Flanigan, op. cit., pp. 131-140

[28] I will here use empirical evidence about the current regulatory regime in the US to assess the plausibility of Flanigan's proposal. See Jeffrey N Gibbs, and Bruce F Mackler, 'Food and Drug Administration Regulation and Products Liability: Strong Sword, Weak Shield', *Tort & Insurance Law Journal* (1987): 194-243.

[29] Tomas J Philipson, and Eric Sun, 'Is the Food and Drug Administration Safe and Effective?', *Journal of Economic Perspectives,* 22 (2008): 85-102.

[30] Assuming that American courts will follow its actual practice, under Flanigan's certification system, it will be equally difficult for plaintiffs to successfully sue companies for something other than defective manufacturing or labelling, since positive certification provides a strong line of defence for the firm regarding design and testing. See Steven Garber, *Product Liability and the Economics of Pharmaceuticals and Medical Devices* (Rand Corporation, 1993).

[31] Joseph A DiMasi, Henry G Grabowski, and Ronald W Hansen, 'Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs', *Journal of health economics,* 47 (2016): 20-33. Richard Nagareda, 'Mass Tort Litigation in a World of Settlement', (Chicago: Oxford University, 2007).

[32] See Carl F Cranor, *Regulating Toxic Substances: A Philosophy of Science and the Law* (Oxford University Press on Demand, 1997). Richard B Stewart, 'Regulatory Compliance Preclusion of Tort Liability: Limiting the Dual-Track System', *The Georgetown Law Journal,* 88 (1999): 2167. As a matter of fact, when such cases go to court, the verdict may easily contradict the FDA approval decision –see M.D. Green, 'Safety as an Element of Pharmaceutical Quality: The Respective Roles of Regulation and Tort Law', *St. Louis University Law Journal*, 42 (1997): 163. The historical record suggest that endless litigation with unsatisfactory outcomes for both parties was already a concern in the passage of the original 1906 Pure Food and Drug Act: see I. D. Barkan, 'Industry Invites Regulation: The Passage of the Pure Food and Drug Act of 1906', *American Journal of Public Health,* 75 (1985): 18-26.

[33] K. Willis, 'Anticipating a Vioxx defense strategy'. *Tort Trial & Insurance Practice Law Journal*, 41.4 (2006): 1163-1178.

[34] Garber, op. cit., pp. 32-35.

[35] Garber, op. cit., pp. 38-42.

[36] A reviewer observes that I am scaling up here the use of Ulysses contracts from an individual to a societal level. But predictably, not every member of a society will be happy to subscribe it, creating difficult situations for paternalist authorities. This is a real problem that unfortunately I cannot cover here.

[37] J. Reiss, 'Meanwhile, Why Not Biomedical Capitalism?', in K. Elliott & D. Steel (eds.), *Current Controversies in Science and Values* (New York: Routledge, 2017), pp. 161-75

[38] Edward L Glaeser, and Andrei Shleifer, 'The Rise of the Regulatory State', *Journal of economic literature,* 41 (2003): 401-25.

[39] Jesús Zamora, 'The Economics of Scientific Knowledge', in U. Mäki (eds.), *Handbook of the Philosophy of Science: The Philosophy of Economics* (Amsterdam: Elsevier, 2011), pp. 759-98.

[40] Jesús Zamora, 'Scientific Inference and the Pursuit of Fame: A Contractarian Approach', *Philosophy of Science,* 69 (2002): 300-23.

[41] David Teira and Jesús Zamora, 'The Politics of Positivism: Disinterested Predictions from Interested Agents', in U. Mäki (ed.), *The Methodology of Positive Economics: Reflections on the Milton Friedman Legacy* (Cambridge: Cambridge University Press, 2009): pp. 189-214.