*Regulation & Governance* (2021) 15, 969–986 doi:10.1111/rego.12360

# The ratio of vision to data: Promoting emergent science and technologies through promissory regulation, the case of the FDA and personalised medicine

Stuart Hogarth

*Department of Sociology, University of Cambridge, Cambridge, UK*

Paul Martin

*Department of Sociological Studies and iHuman, University of Sheffield, Sheffield, UK*

**Abstract**

Pharmacogenetic tests provide genetic data to tailor drug treatment and were widely predicted to be one of the first fruits of the Human Genome Project. In the mid-2000s, the US Food and Drugs Administration (FDA) became an advocate for pharmacogenetic testing, but its efforts to build a market for this new technology brought the agency into dispute with other regulatory actors over the type of evidence needed for the adoption of pharmacogenetic testing, in particular the importance of randomized control trials. The warfarin case highlights the tension between a new form of promissory regulation driven by future expectations and FDA's established role as protector of public health; and the controversy can be conceptualized as a struggle over regulatory epistemologies within a complex polycentric regulatory space. Our case study addresses two themes central to the burgeoning scholarship on the governance of emergent science and technologies (EST): the *political economy* of regulation, in particular the role that regulators play in creating markets for EST; and the *epistemological politics* of regulatory science, in particular the controversy that arises when regulators modify scientific standards to accommodate EST. Linking these two themes is the concept of promissory regulation: the idea that regulatory policy may be shaped by an institutional commitment to the transformational potential of EST. This concept sheds new light on the neo-mercantilist nature of contemporary regulatory capitalism.

**Keywords:** FDA, innovation, personalized medicine, pharmacogenetics, randomized control trials, sociology of expectations.

## 1. Introduction

> *"The ratio of vision to data is very high…We love vision, but data is our mainstay." Jerry Collins, Director of the Laboratory of Clinical Pharmacology, US Food and Drugs Administration (FDA). (Hodgson & Marshall, 1998)*
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> *"This first decade of the 21st century began with the decoding of the human genome—a scientific achievement that we knew had the potential to transform our understanding of health and disease and revolutionize our fundamental approach to medicine." Margaret Hamburg, FDA Commissioner, 2010. (Hamburg, 2010)*

In each of these quotes, an official of the US Food and Drugs Administration (FDA) discusses the potential for genomic science to transform drug development and medical practice. The first quote appeared in an article in *Nature Biotechnology*, which reported the skeptical disinterest of pharmaceutical regulators toward the new science of genomics. The second quote from the Commissioner of the FDA suggests that regulatory caution had turned to evangelical zeal. In this article, we explore the political and epistemological challenges faced by FDA as it recalibrated what Collins described as "the ratio of vision to data." Our case study addresses two themes central to the burgeoning scholarship on the governance of emergent science and technologies (EST): the *political economy* of regulation, in particular the role that regulators play in creating markets for EST; and the *epistemological*

Correspondence: Stuart Hogarth, Department of Sociology, University of Cambridge, Cambridge, UK. Email: sh339@cam.ac.uk

Accepted for publication 24 September 2020.

*politics* of regulatory science, in particular the controversy that arises when regulators modify scientific standards to accommodate EBT. Linking these two themes is the concept of promissory regulation: the idea that regulatory policy may be shaped by an institutional commitment to the transformational potential of EST.

### 1.1. The promise of genomics

For over two decades, a chorus of academic scientists and industry executives has promulgated promissory visions of a genomic revolution, predicting a transformation of clinical practice, improvements in human health, and economic benefits from the growth of a new bioeconomy (Hopkins *et al*., 2007). The concept of personalized medicine was adopted by those promoting the vision of a new model of health care in which information about an individual's genetic makeup would be used to improve diagnosis and treatment. By 2004, the largest regulatory agencies governing the development and use of new medicines – the US Food and Drugs Administration (FDA) and the European Medicines Agency (EMA) – had added their voices to the chorus.

Much of this genomic hope was focused on pharmacogenetics: improving the safety and efficacy of treatment by using genetic tests to predict how individuals will respond to pharmaceuticals. The routine use of pharmacogenetic tests in treatment decisions was widely predicted to be the first clinical application of genomic science. FDA promoted the clinical adoption of pharmacogenetic testing through what we term its relabeling project: a systematic effort to add pharmacogenetic data to the labels of drugs that were already in routine clinical use. The relabeling project began in 2003 and although it was only one aspect of FDA's engagement with genomic science, it proved the most controversial. By 2011, agency officials were publicly defending themselves against the accusation that pharmacogenetic relabeling decisions were "arbitrary and/or impulsive" (Zineh & Pacanowski, 2011).

Controversy eventually came to center on our case study: pharmacogenetic testing for the blood-thinning drug warfarin, which many believed could become a poster child for personalized medicine. FDA's relabeling of warfarin in 2007 was hailed by senior figures in the agency as a proof of concept for personalized medicine, but the agency's decision generated controversy, amplifying, rather than resolving, differences of opinion among clinicians, biomedical researchers, and healthcare payors concerning the weight and types of evidence required to support the adoption of pharmacogenetic testing. The epistemological politics of this debate centered on whether the randomized control trial (RCT) would remain the gold standard of clinical evidence in the genomic era.

In previous work, we have outlined FDA's deepening commitment to genomic science as part of a wider vision for a paradigm shift in the development and regulation of pharmaceuticals (Hogarth, 2012; Hogarth, 2015). This vision was articulated in 2004 when FDA released a wide-ranging report, which positioned the use of genomics at the heart of a broader regulatory reform agenda (FDA, 2004). The critical path report addressed the declining productivity of drug development by suggesting that pharmaceutical firms were failing to exploit rapid advances in genomic (and related) sciences. The report situated the agency as a key actor in the creation of a new regulatory science and a new product development toolkit. It was the first programmatic statement of a shift in FDA's role in the biomedical innovation process, from gatekeeper to enabler of innovation.

FDA's embrace of genomics occurred under the Bush administration and was in part driven by Bush-appointed FDA executives pursuing a deregulatory agenda focused on reducing evidentiary requirements in order to accelerate (and reduce the cost of) drug development (Hogarth, 2015). The 2004 Critical Path report was thus simply the latest phase in what Davis and Abraham (2013) have described as the era of *permissive regulation* that had begun during the Reagan administration. In previous work, we have argued that genomics provided a new scientific rationale for deregulation and we characterized this confluence of deregulatory politics and genomic science as a form of neoliberal technocracy (Hogarth, 2015). In this article, our focus on FDA's relabeling project shifts the analysis from policy development to policy implementation, and our theoretical framework expands to explore the relationship between permissive regulation and promissory regulation.

In this article, we argue that FDA's promotion of pharmacogenetics manifested the agency's transformation from gatekeeper to enabler of innovation and its advocacy was a form of *promissory* regulation. This new role entailed not simply the promotion of pharmacogenetics as a new form of regulatory science, but advocacy for specific clinical applications of this approach. FDA thus shifted from regulating established markets to building a new market for an emergent class of biotechnologies. FDA's enthusiasm for genomics reflects the pervasive appeal of biotechnology to powerful actors in science, industry, and government across the world. As Jassanof

 

has noted, in Europe and the United States, the birth of a new bioeconomy was driven by "firm national commitments to basic science, economically powerful industries, and state authorities eager to demonstrate their support for a winning technology" (Jassanoff, 2005, p. 66).

We make two key theoretical contributions at the intersection of regulatory governance scholarship and science and technology studies (STS). Firstly, we advance the sociology of expectations by revealing how regulatory agencies can become the promoters of new sociotechnical imaginaries. We thus extend the concept of promissory science to encompass the practice of *promissory regulation*. Secondly, we explore the politics of knowledge production in the context of an emergent biotechnology. The warfarin controversy was a contest over *regulatory epistemologies*, the frameworks of knowledge production that legitimize regulatory decisions. Finally, our exploration of epistemological politics illuminates the polycentric structure of the regulatory regime, in particular the gatekeeping roles played by different actors in the postmarket approval space. We thus extend the political sociology of pharmaceutical regulation, in particular our understanding of the contemporary era of permissive regulation (Davis & Abraham, 2013). The warfarin controversy offers new insights into how regulatory agencies are reconceptualizing their role in the biomedical innovation system; how their power is legitimated by regulatory epistemologies, and the diffuse networks of power operating in the regulatory space.

## 2. Background and conceptual framework

### 2.1. Promissory regulation

Processes of standard setting are intrinsic to the practice of contemporary biomedicine; they are "a condition for the production, circulation, and interchangeability of novel entities and practices" (Keating & Cambrosio, 2003, p. 332). As emergent biotechnologies move from the laboratory to the clinic, regulation plays a crucial role in the process, addressing commercial uncertainties about the path to market and public anxieties about safety and ethics (Faulkner, 2012). However, FDA's engagement with personalized medicine went beyond the role of regulatory arbiter to encompass a new role as technology advocate.

To understand this development, we draw on the sociology of expectations, a body of scholarship that has explored how future-oriented visions help to constitute new fields of research, playing a key role in the enlistment of support, the mobilization of resources, and the shaping of technological artifacts (Brown & Kraft, 2006). Specific expectations can become embedded in the design of experiments and funding programs (Hedgecoe & Martin, 2003), playing a performative role in constructing the future (Borup *et al*., 2006). However, not all such envisioned futures come to pass, and emergent fields of science and technology are often marked by cycles of hope and disappointment (Brown, 2003), particularly as they are enacted through specific technological applications (Borup *et al*., 2006).

The literature on promissory science has until recently focused on the activities of those engaged in innovation – scientists and high-tech firms – however, Pollock and Williams (2010) have analyzed the promissory role of industry analysts in fields such as IT. Market analysts function as intermediaries, occupying a position in between producers and consumers of emergent technologies, and playing a pivotal role in shaping sociotechnical expectations through the production of "future-oriented research." Pollock and Williams describe such market intermediaries as "promissory organizations."

Here, we suggest that pharmaceutical regulatory agencies share key functional characteristics of promissory organizations: neither producers nor consumers, they sit between the manufacturer and the market. As it promoted genomic science, FDA, like other promissory organizations, was engaged in the business of shaping and building markets. However, unlike industry analysts, the intermediary status of the FDA is predicated on its role as gatekeeper empowered to decide which products move from R&D onto the market. There is an inevitable tension between *shaping* a market through the formally neutral role of regulatory arbitration of technological options and *building* a market through technological advocacy.

Abraham and Davis (2007) argued that in pharmaceutical regulation, "hopes" and "promises" may conflict with the demand for evidence, and in certain circumstances, promissory science can have a negative impact on regulatory precaution. Moreira and Palladino (2005) have characterized this as a conflict between two regimes with distinct temporal orientations: the future-oriented regime of hope in which scientists, firms, and patient groups focus on the expected benefits of new technologies; and the present-oriented regime of truth in which

 

regulators evaluate the current state of evidence. FDA's advocacy for genomics re-situated the agency in a liminal space between the regimes of hope and truth. Senior FDA officials used their institutional power to gain a critical position in articulating future visions about personalized medicine in the United States, but as this was enacted through specific regulatory decisions, other actors criticized the agency for a lack of scientific rigor. Understanding the dynamics of this controversy requires a conceptual analysis of the nature of the regulatory space of contemporary biomedicine.

### 2.2. Epistemic authority and regulatory power

FDA practices regulatory science, its legal powers enshrined in statute, and its epistemic authority manifested in scientific standards that define what counts as valid evidence. Carpenter (2010) suggested that FDA's regulatory power and epistemic authority have three dimensions: directive, gatekeeping, and conceptual.

*Directive* power is the exercise of legal measures by the FDA over industry – it may take the form of an instruction to change a manufacturing process or to add a warning about adverse events to a drug label. FDA's *conceptual* power refers to its ability to shape the institutional framework of pharmaceutical R&D. The 1962 Kefauver Amendments empowered FDA to establish the three pillars of the contemporary pharmaceutical regulatory regime: premarket review of drugs to evaluate their safety and effectiveness, the three-phase sequence of clinical studies, and the requirement that the final and largest study (Phase III) should be an RCT. FDA did not invent the RCT, but by making it a mandatory requirement for approval of new drugs, the agency played an important role in elevating it to its current status as the gold standard of clinical evidence. In turn, FDA's adoption of the RCT bolstered the agency's *epistemic authority*, legitimizing its practice of regulatory science.

Industry had to comply with the new regulatory regime because the 1962 Kefauver Amendments reinforced FDA's gatekeeping role. *Gatekeeping* power describes FDA's role in the evaluation and market approval of medical products, its function as an obligatory point of passage between the premarket space of clinical research and the postmarket space of clinical practice. The gatekeeping role is the foundation of FDA's power, but it also establishes the limits of that power, which resides mainly in the premarket space. Once a product has received market approval FDA's power is limited, a weakness exemplified by its inability to enforce completion of postmarket clinical studies (Darrow *et al*., 2020). FDA has a variety of regulatory implements in its postmarket toolbox, but it has increasingly come to rely on relabeling medicines as the principal means of addressing postmarket issues. However, a 1997 survey revealed that 85% of US doctors stated that FDA labels have "little" or "practically no influence" on their treatment decisions (Beck & Azari, 1998) and off-label use of drugs is routine and in effect unregulated by FDA (Chen *et al*., 2009).

Much scholarship on pharmaceutical regulation focuses on the role of agencies such as FDA which license market access, but it would be wrong to characterize postmarket space as a regulatory vacuum. Carpenter is typical in his neglect of other actors, who figure in his model only as potential objects of regulation, not as regulatory actors themselves (see Carpenter, 2010, pp. 586–587). In contrast, we characterize postmarket space as a polycentric regulatory regime.

Other actors in the postmarket space include patient advocacy groups (Epstein, 1996) and the courts, which are a venue for scrutiny of regulatory violations such as bribery and off-label promotion (Jasanoff, 1994; Braithwaite, 2013). Such actors may function as 'countervailing powers' (Abraham, 2007; Gabe *et al*., 2012). However, our focus is on postmarket actors who perform a gatekeeping function, influencing the scale and pace of adoption of new medical technologies, and who are often collectively referred to as the 'Fourth Hurdle', reflecting their gatekeeping power. Social scientists are increasingly interested in the Health Technology Assessment (HTA) movement (Faulkner, 1997; Ozieranski *et al*., 2012; Löblová *et al*., 2020). HTA emerged in the 1970s in response to concerns that new medical technologies were entering clinical practice fueled by optimistic and often unquestioning acceptance, rather than formal evaluation of evidence. HTA established a new knowledge production process concerned with "the field-testing of the effectiveness and cost-effectiveness of healthcare technologies" (Faulkner, 1997). The rise of HTA is coterminous with the emergence of evidence-based medicine (EBM) and the growing importance of clinical practice guidelines as another mechanism for the systematic evaluation of medical technologies. In the United States alone, it has been estimated that 1,000 new guidelines are produced

 

each year by "professional societies, public-sector agencies, research organizations, health care insurers, health maintenance organizations, and individual health care institutions" (Timmermans & Berg, 2010, p. 7).

There is thus a profound temporal and spatial bifurcation in the operation of power within the pharmaceutical regulatory regime. In the premarket space, legal power is exercised by FDA over industry according to the traditional model of command-and-control regulation, but in the postmarket space power is diffuse, not only is the regulatory agency's legal power much weaker, but the role of gatekeeper to the clinic is shared among multiple actors.

The growing literature on HTA, EBM, and clinical practice guidelines illustrates the polycentric (Black, 2008) structure of postmarket space and the variety of gatekeeping processes that shape the scale and pace of clinical adoption, but hitherto there has been little research on the interactions between FDA and postmarket gatekeepers. The dispute we analyze here hinges on what we term regulatory epistemologies. In the postmarket space, a range of actors ask diverse questions about the safety, effectiveness, and economic cost of medical technologies, each informed by their specific interests in governing technology diffusion. What unites these actors is a preference for epidemiological evidence generated through clinical research,[1] over mechanistic knowledge produced in laboratories, and their commitment to the RCT as the most reliable method for conducting clinical research. Biomedical researchers began to adopt the RCT decades before it was championed by FDA (Marks, 1997), and the emergence of HTA and EBM has served to consolidate its pre-eminent status (Lehoux, 2006).

The RCT may be the gold standard but it is not hegemonic. Of direct relevance for our case, RCTs are not typically required for the approval of diagnostic tests, and FDA frequently uses non-randomized studies to support drug labeling claims regarding dosing for different patient subgroups. Moreover, the RCT is less central to drug development than it once was: in the two decades between 1995 and 2017, the percentage of drugs approved without RCT data increased from 4% to 17% (Darrow et al., 2020), clear evidence of the deregulatory trend of permissive regulation.

## 3. Methods

Our initial research in this area was conducted between 2004 and 2008. Desk research took the form of a literature review encompassing regulatory guidance documents, scientific papers, and grey literature including policy reports, industry surveys, and industry news publications. Field research took the form of 15 expert interviews with industry executives, regulatory officials and clinicians, and participation in four scientific meetings and industry conferences. Subsequent participation in industry/scientific conferences and policy fora in Europe, North America, and Japan have provided further opportunities to garner evidence on the elaboration of public policy and commercial strategy in this area. In 2012, we supplemented this field work with four additional interviews with industry and regulators and conducted a further literature review of outputs from regulatory agencies including new guidance documents, regulatory decisions, minutes and transcripts of regulatory advisory committees, presentations to conferences and media interviews, and other gray literature and scientific papers. These various data sources have been carefully reviewed to provide a detailed timeline of events. Interview transcripts have been analyzed with this in mind to help triangulate and give depth to the narrative.

Our analytic approach draws on two traditions. The first is in the tradition of case study, policy analysis, and historiography, which dictates data comprehensiveness, context-specificity, and a reflexive and critical interpretive stance to generate a holistic portrait of a policy or organization (Patton, 2002; Yin, 2009) to provide data generalizable to theoretical propositions (Eisenhardt, 1989). Our second qualitative approach is in the tradition of constructivist grounded theory, whose subject matter is interaction and meaning (Straus & Glaser, 1967). This tradition supports interpretive thematic analysis of the beliefs, commitments, and rationales that underlie practices (Kvale, 1996). It offers a structured methodology for developing and organizing the categories of practices and meaning, as well as guiding data collection.

## 4. Promise and controversy

In August 2007, senior FDA officials held a press conference to announce an update to the product label for the blood-thinning drug warfarin. The label would now include the information that individual differences in

 

response to the drug are in part the result of variations in patients' genetic make-up. Revising drug labels is a routine regulatory process; most months FDA will make at least 20 such updates. Seldom are label revisions announced by senior FDA officials, or publicized via a press conference. What made this update different? FDA's press release highlighted the public health implications: warfarin is a widely used drug with a narrow therapeutic index – the margin between too high a dose and too low a dose is slim – and the consequences of over- or under-treatment can be severe: "Warfarin is the second most common drug – after insulin – implicated in emergency room visits for adverse drug events" (FDA, 2007a). Much of the danger, the press release explained, arises at initiation of treatment – individual dose tolerance varies, so doctors must establish the correct dosage gradually by measuring whether the patient's blood is clotting properly. The agency theorized that knowing an individual's genetic makeup could help doctors to more quickly establish the correct dosage for each patient. As FDA Commissioner Andrew von Eschenbach made clear, it was the use of *genetic* data which made the label revision a milestone in FDA history:

> *Today's approved labeling change is one step in our commitment to personalized medicine. By using modern science to get the right drug in the right dose for the right patient, FDA will further enhance the safety and effectiveness of the medicines Americans depend on (FDA, 2007a, p. 2).*

The press conference was held four years into FDA's relabeling project, which began shortly after the complete sequencing of the human genome in April 2003, a scientific achievement the US Secretary for Health and Human Services Tommy Thompson described as "momentous…the dawn of a new era in medicine and biology" (Thompson, 2003). In the same month, FDA Commissioner Mark McClellan set out the implications for therapeutic innovation: "New therapies will be developed with genetic or phenotypic tests that can identify an appropriate treatment population and detect patients who need different doses or are prone to certain toxic effects" (McClellan, 2003). A few days after that article was published, a new FDA advisory committee met to consider how the agency might enact McClellan's grand vision by helping to bring pharmacogenetic testing into clinical practice.

The Clinical Pharmacology Subcommittee of FDA was an offshoot of the Advisory Committee for Pharmaceutical Science. It would become an important vehicle for FDA's relabeling project, reviewing the evidence for relabeling proposals and making recommendations to the agency about whether and how to relabel. Setting out the agenda for the inaugural CPS meeting was Larry Lesko, Director of the Office of Clinical Pharmacology and Biopharmaceuticals and one of FDA's most prominent advocates for pharmacogenetics. Lesko explained that the agency was keen to exploit genomics as part of a broader initiative to improve drug safety, but he described pharmacogenetics as "a work in progress." Chief among the issues yet to be resolved was the evidentiary standards to support label revisions:

> *…as we talk about including genetic information in the label for the purpose of drug dosing, in the discussion and debate about that, frequently people will ask what is the evidence…[this] is something we have to think very clearly about. (FDA, 2003, p. 25)*

Lesko suggested that prospective RCTs might be infeasible, since it was unclear who would conduct the research, and so relabeling might rely on other forms of evidence, such as systematic reviews of academic studies or expert opinion. This evidentiary uncertainty was to become a major stumbling block for FDA's relabeling project.

In 2003, FDA relabeled the cancer drug 6-mercaptopurine thiopurine to indicate the increased risk of adverse events as a result of interindividual variation in the TPMT genotype. In 2006 another cancer drug, Irinotecan, was relabeled to warn of pharmacogenetic risks, this time associated with the UGT1A1 gene. By FDA's own admission, in neither case did these initial efforts at relabeling have significant impact on clinical adoption of pharmacogenetic testing (Lesko & Zineh, 2010). Laboratory directors, a key group for the successful adoption of new diagnostic tests, complained that pharmacogenetic data label updates were insufficient to guide dosing decisions and thus raised legal liability concerns. These issues were made clear by Debra Leonard, a leading molecular pathologist, during a meeting of the Secretary's Advisory Committee on Genetics, Health and Society (SACGHS):

 

*From a liability perspective, it's kind of disturbing to have some labelling that says, and you may want to think about doing this because these polymorphisms affect dosing. Okay. So you do the test. Then what? And if you don't do the test with that on the label, where are you? So you're kind of between a rock and a hard place. (Leonard quoted in SACGHS, 2006, p. 77)*

The HTA community was also sceptical, an attitude exemplified by an evidence review on UGT1A1 testing conducted by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group:

*The clinical utility…is unknown. No study has prospectively documented the potential benefits (reduced adverse drug events) or harms (reduced proportion of responsive tumors). (Palomaki* et al.*, 2009)*

EGAPP's review was published in 2009 but clinical resistance and HTA skepticism were already a well-established response to pharmacogenetic testing, as exemplified by the fate of Roche Molecular's Amplichip test. Approved by FDA in 2004, the Amplichip targeted the CYP450 genes, which influence metabolism of many commonly prescribed drugs. CYP450 testing could, in theory, guide dosage decisions by identifying likely poor metabolizers and rapid metabolizers. However, Amplichip was a commercial failure. A succession of HTA reports found insufficient evidence of clinical utility to support adoption. The Blue Cross policy decision was typical, stating that CYP450 testing should be considered 'investigational/not medically necessary' because "Clinical utility studies for genotyping for well-established brand name and generic drugs are in their infancy" (BlueCross BlueShield Association, 2004).

Following the failure of the Roche Amplichip, some industry figures suggested that state support was needed to create a market for pharmacogenetic testing. Kari Parukkeri, CEO of the diagnostics company Jurilab, suggested that demand would only grow if FDA produced a mandatory relabeling recommendation, explicitly requiring pharmacogenetic testing for a drug (Womack, 2005). That industry was looking for leadership from FDA to build a market for pharmacogenetic tests, indicates the degree to which the agency was now viewed as an enabler of biomedical innovation and an advocate for personalized medicine. A clear division had emerged between the regime of hope, populated by advocates promoting pharmacogenetic testing as an exemplar of personalized medicine, and the postmarket gatekeepers occupying the regime of truth, who treated pharmacogenetics as simply another technology.

### 4.1. Warfarin – Poster child or problem child?

The prospect of stronger pharmacogenetic relabeling guidance came in November 2005 when the Clinical Pharmacology Subcommittee recommended that FDA relabel warfarin. The committee agreed unanimously that there was sufficient evidence to recommend lower doses of warfarin for patients with genetic variations in the CYP2C9 and VKORC1 genes, and that genotyping patients in the induction phase of warfarin therapy would reduce adverse events and reduce time to stable dosing. A scientist who participated in the meeting welcomed this as a major breakthrough:

*FDA-approved tests have very fuzzy labels…but the one for Warfarin will be a much stronger recommendation – the meeting was unanimous – when FDA's label change comes out in the summer it will be widely picked up. (Interview with US scientist, 2006)*

The potential impact on commercialization was signaled by the Canadian diagnostics firm Tm Bioscience in 2006, when it announced that it was developing a warfarin test and cited the relabeling recommendation as an example of how FDA decisions were driving the pharmacogenetics market. Other industry executives were less optimistic about the transformative potential of warfarin. An executive at a leading US genetics laboratory reported that market research showed doctors would be slow to adopt warfarin pharmacogenetics. They also predicted that the FDA label update would not be directive as some hoped, but would resemble prior revisions, another 'fuzzy label' offering information but not demanding action (USA exec 1, 2006).

Why did so much hope come to rest on the relabeling of warfarin? As FDA officials indicated at the 2007 press conference, it is a widely prescribed drug and a leading cause of serious adverse events. Establishing the optimal dose for an individual patient can take weeks of careful monitoring using prothrombin time (PT) testing, and during this period there is a high risk of adverse events. In a review article, Kirchheiner (2004, p. 73)

 

highlighted warfarin's potential as a putative poster child for pharmacogenetics, concluding that it was "most likely to be the first example of CYP2C9 genotyping in clinical practice." Papers by two other leading pharmacogenetic researchers echoed this view (Daly, 2005; Pirmohamed, 2006). In 2005, a systematic review and meta-analysis confirmed the role of genetics in warfarin metabolism and risk of bleeding, and the potential benefits of pharmacogenetic testing. However, the authors concluded that "Evidence for the clinical utility and cost-effectiveness of genotyping is needed before routine testing can be recommended" (Sanderson *et al*., 2005). Kircheiner and Daly's papers also highlighted the need for prospective trials.

Prior to relabeling, FDA responded to this call for more evidence in 2006 when it published a list of Critical Path priority challenges. The report outlined key elements in FDA's strategy for implementing its vision of a new genomic-based regulatory science and singled out warfarin as an example of how pharmacogenetic testing could improve drug safety. Media reports stated that FDA would provide up to $750,000 for a prospective trial for "the development and clinical validation of a 'genotype-driven warfarin dosing algorithm'" (Womack, 2006).

Five months after the advisory committee recommendation for a relabeling of warfarin, FDA were approaching the issue as a research challenge, aligning with those in the scientific community who highlighted warfarin as a highly promising candidate for pharmacogenetic testing, but one that still required RCT evidence demonstrating improved outcomes.

### 4.2. Warfarin relabeled

FDA's warfarin relabeling eventually came in August 2007, 20 months after the committee's recommendation, but it was not as radical as some had hoped. The new label stated that *CYP2C9* and *VKORC1* genotypes may be useful in determining the optimal initial dose of warfarin and provided a range of doses if the genotypes were known, but FDA provided neither precise dosing recommendations nor an explicit recommendation for genotyping. The press conference to announce the decision was led by Larry Lesko and Janet Woodcock, Deputy Commissioner, and Chief Medical Officer of FDA.[2] Opening the conference Lesko highlighted that this was the first time a widely used drug had been relabeled to include genomic data in the dosing information (FDA, 2007b). However, Woodcock struck a note of caution, stressing that further research was required:

> *…there's a fair amount of work that would have to be done before the biomedical community would determine whether or not this would be considered part of standard therapy or not…this is right now just one of the factors to consider when dosing warfarin. (FDA, 2007b, p. 18)*

Crucially, FDA had not provided clear practical guidance on how to change patient treatment based on pharmacogenetic data, as Lesko acknowledged: "Although genetic testing can currently identify who has these genetic variants, more studies are needed to explore the precise starting dose for these patients" (FDA, 2007a). FDA, he explained, had been working on this with the Critical Path Institute (CPI), an organization established at arm's length from FDA to broker public-private partnerships on Critical Path projects. CPI was working with the University of Utah, the National Heart, Lung and Blood Institute and Harvard Partners on new trials and development of guidance on pharmacogenetic-based dosing for warfarin.

Lesko also expressed reservations about pushing testing too aggressively since access to testing might still be limited, given the absence of FDA-approved diagnostics. A journalist named John Rikert responded to these notes of caution by questioning the consistency of FDA's stance:

> *Well don't you think that as the results of this press conference there is going to be a great demand for these tests and that you really want it both ways? You're saying hey these tests are here, but we don't know whether you should use them or not?. (FDA, 2007b)*

Challenged on the gap between vision and data, Lesko defended FDA's decision, arguing that they had an obligation to share the information about warfarin pharmacogenetics with doctors and patients. The exchange suggests that two evidentiary standards were at work: the first threshold was whether FDA had sufficient evidence concerning the genetics of warfarin metabolism to justify updating the drug label, because to withhold such data from users of the drug would be unethical. The second evidentiary threshold was whether FDA had sufficient data to push for a change in clinical practice, by providing clear dosage guidance based on evidence from RCTs.

 

As Rikert implied, FDA's decision to relabel warfarin was not in itself controversial, but by seeking national media coverage for the decision, and presenting it as a landmark moment in the agency's promotion of personalized medicine, the FDA had raised the stakes; this was not a routine relabeling. Media skepticism about the disjuncture between the claims being made for the significance of the decision and the admission of evidentiary gaps prefigured widespread disagreement with the warfarin label update.

### 4.3. Resistance and skepticism

FDA's decision to relabel warfarin amplified, rather than resolved, differences of opinion concerning the weight and types of evidence required to support the adoption of pharmacogenetic testing. In December 2007, the *Harvard Health Newsletter* published an article about warfarin pharmacogenetics. Its opening line summarized its sceptical message: "There's little evidence yet that a genetic test improves the safety of warfarin." Pharmacogenetic testing it concluded "may well be the wave of the future. For warfarin, right now, it's barely a ripple" (Anonymous, 2007). The briefing offered a succinct summary of the key issues, which would define the ensuing controversy: the lack of evidence that testing would improve outcomes; the possibility that it might in practice worsen outcomes; and concerns about cost-effectiveness .

Further evidence of clinical skepticism came in 2008 in guidance from two professional bodies. The American College of Chest Physicians' revised anticoagulation management guidelines stated that: "[We] suggest against pharmacogenetic-based dosing until randomized data indicate that it is beneficial" (Ansell *et al*., 2008). The American College of Medical Genetics also highlighted the lack of utility data, suggesting that despite good evidence that genetic markers could predict stable warfarin dosage "the evidence seems weak for any association between *CYP2C9* testing and severe bleeding events" (Flockhart *et al*., 2008, p. 149).

Healthcare payors also weighed in to the controversy. In 2008 Blue Cross Blue Shield, a major healthcare insurer, deemed warfarin pharmacogenetics as "investigational," a term used for health technologies which are either not FDA-approved or lack evidence that they improve health outcomes.[3] They acknowledged that "Genetic testing may help predict the initial warfarin dose within the first week of warfarin treatment…" a point which would appear to have had universal support, but, like other skeptics, they cited the lack of evidence that pharmacogenetic testing could improve clinical outcomes (BlueCross BlueShield of North Carolina, 2008). Aetna, another major US healthcare insurer, came to a similar conclusion (Aetna, 2007).

Despite this controversy, warfarin testing attracted high-level political support. In 2008, the US Health Secretary singled out the hopes attached to warfarin in the opening pages of his second report on personalized medicine: "If genetic tests can improve initial dosing of warfarin, the savings in health and dollars will be substantial: one estimate is over $1 billion per year" (US Department of Health and Human Services, 2008). Further support came from the molecular diagnostics industry. At the 2007 relabeling press conference, Lesko stated that FDA was encouraging companies to submit tests for approval, and by 2009 five firms (Osmetech, Autogenomics, TrimGen, Paragon Dx, and Nanosphere) had responded to this entreaty.

With industry now supplying a range of technological options for pharmacogenetic testing, the main obstacles to clinical adoption were positive coverage decisions by health insurers and endorsement in clinical guidelines. A year after FDA's relabeling decision, the Center for Medicare and Medicaid Services (CMS), the body responsible for Federal healthcare delivery, launched a public consultation on whether it should cover warfarin testing. The process revealed a divergence of opinion surrounding the issue. The American Association for Clinical Chemistry and the College of American Pathologists, two professional bodies representing pathologists, were in favor, but opposing coverage were two bodies representing clinicians: the American Heart Association and the American Society for Hematology, as well as the pathology body with greatest expertise in genetic testing - the Association for Molecular Pathology. Blue Cross Blue Shield also responded, reiterating its argument that large, well-designed RCTs were needed. Seventeen months after launching the consultation, CMS published its decision: more data were needed, so warfarin pharmacogenetic testing would be available to CMS patients only under their Coverage with Evidence Development program, that is, only for patients enrolled in prospective RCTs comparing pharmacogenetic-guided dosing with standard dosing strategies (CMS, 2009).

 

*4.3.1. The uncertainty principles*

At this stage in the narrative, it might be useful to take stock of developments. Warfarin had become an exemplar for personalized medicine and had high-level political support. Advocates and sceptics seemed willing to agree on a number of points: warfarin is a major cause of serious adverse events; improving the safety of warfarin patients is important; interindividual variation in dosing response has a genetic component; and warfarin pharmacogenetic testing would require clear dosing guidance. Yet the warfarin relabeling intensified the division between FDA and gatekeepers to the clinic, highlighting the polycentric structure of postmarket regulatory space.

The controversy articulated two very different ways of *framing uncertainty*: those who supported the relabeling decision focused on the time it took to reach a stable, safe dose using PT testing. In contrast, sceptics focused on the uncertainty about pharmacogenetic testing: whether it would accelerate time to stable dosing, reduce adverse events and be cost-effective. Exemplifying the practice of promissory regulation, the relabeling decision indicated FDA's greater appetite for *embracing uncertainty*, a readiness to give the benefit of the doubt, rather than a skepticism about doubtful benefits.

The conflict revealed fundamental differences about the evidence required to enable the adoption of warfarin pharmacogenetics testing in the clinic. This point was made clear by Lesko at the CPS meeting which recommended relabeling warfarin:

> *…frequently in revising labels we lack perfect evidence, for a specific dose reduction for example, but we feel this is not a reason to support inaction when we have a preponderance of evidence that supports safety or efficacy or improved dosing. (FDA, 2005, p. 16)*

Given FDA's own acknowledgement of the need for more data, there was at this stage both ambivalence about the RCT-based regulatory epistemology, and an ambiguous elision of the evidentiary standard that might justify updating a drug label to inform doctors about pharmacogenetic factors, and the data needed to change medical practice.

The division entrenched the emergent epistemological divide on how best to go about *resolving uncertainty*. All parties were agreed that more evidence was desirable and, given that CMS was willing to pay for warfarin pharmacogenetic testing carried out as part of an RCT, some payors were willing to countenance a controlled diffusion into clinical practice. Their disagreement centered on the scale and nature of experimental diffusion. Consistent with its championing of real-world observational data (see later), FDA advocated rapid and widespread adoption for all new warfarin patients. In contrast, consistent with their preference for carefully controlled RCTs, CMS preferred a far more limited regulatory experiment.

### 4.4. More evidence, more arguments

Clinical evidence on warfarin pharmacogenetic testing was accumulating from 2007, but this did not lead to closure of the debate; rather it further entrenched the existing divisions, particularly around what *type* of data was acceptable. The Couma-Gen study was an RCT supported by the Critical Path Institute (CPI). Ray Woolsey, President of the Institute, had described Couma-Gen as the "first serious effort to prospectively, rather than retrospectively, develop and validate a pharmacogenomic method for treating patients" (cited in Womack, 2006). Its results were published in 2007 soon after FDA's relabeling decision: although the combination of pharmacogenetic and clinical factors provided an initial dose more closely predictive of the stable maintenance dose, the paper concluded that if good practice was adopted in the management of patients through conventional PT testing then pharmacogenetic testing did not add significant value (Anderson *et al*., 2007).

This CPI-supported study provided a serious challenge to warfarin pharmacogenetics advocates and FDA's response was indicative of how much political capital was now invested in the promotion of warfarin as an exemplar for personalized medicine. In 2008, Larry Lesko and Brian Gage, a leading authority on warfarin pharmacogenetics, published a paper rebutting the Couma-Gen findings. They argued that the study's results had been misreported in public comment with undue emphasis on its negative aspects, but they also identified multiple technical faults with the paper. They concluded by highlighting that more warfarin trials were underway, suggesting that it was only a matter of time before supportive data was forthcoming (Lesko & Gage, 2008). Lesko

 

published a further piece the same year as part of a debate on the pros and cons of warfarin pharmacogenetics. He offered a checklist of points on which the Couma-Gen paper supported use of genetic testing and concluded:

> *The question about warfarin pharmacogenetics before us now is not 'is it ready for prime time?' The more important question is, while more and more studies are being planned and/or conducted, should we accept and use our current knowledge about genetic factors to improve the quality of warfarin initial dosing and anti-coagulation in our patients. The benefits and risks of pharmacogenetics, in my view, favor pharmacogenetics (Lesko, 2008, p. 303).*

Again we see a continued ambivalence from FDA – at the time of relabeling warfarin, the agency heralded the decision as a proof of concept for personalized medicine, but then acknowledged major evidence gaps. Now Lesko was advocating the adoption of pharmacogenetic testing while conceding it was not "ready for prime time" given the continued evidence gaps. In 2007, Lesko had rebutted criticism of the warfarin relabeling by citing FDA's duty to share genetic information with clinicians; now he shifted the ethical obligation on to clinicians, arguing that the need for more data was not an excuse for rejecting warfarin pharmacogenetics. Lesko's argument for implementation ahead of new data assumed that future evidence would vindicate his position, an optimism characteristic of the regime of hope.

### 4.5. Medco/Mayo – A new paradigm?

In 2010, publication of the results from another warfarin pharmacogenetics study (Epstein *et al*., 2010) marked a decisive shift in the terms of the controversy: from arguments about the need for *more* data to disputes about the *type* of evidence required. The Medco/Mayo study started in 2007 and was a collaboration between the Mayo Clinic, a leading center for clinical research in the United States, and the pharmacy benefits company Medco. The study was not an RCT but had two arms: genotyped patients and non-genotyped patients, and the hospitalization rates for genotyped patients were 31–44% lower than those who were not genotyped. The authors of the paper described their research as the first "nationwide prospective study examining outcomes" in "real-world' settings." However, the paper was accompanied by a letter and editorial criticizing the lack of randomization, which may have introduced bias through confounding factors. These critics pointed out that other trials which were currently underway were randomized and suggested that the Medco/Mayo study could easily have been randomized too. The authors of the paper defended their study design by stating that they wanted to conduct research on how pharmacogenetics could improve warfarin dosing in typical practice settings, a clear contrast to the Couma-Gen study.

The debate about the value of the gold standard RCT had begun before the publication of the Medco/May study data, with senior FDA officials increasingly emphasizing the value of observational studies compared with RCTs. In a 2009 feature in *CAP Today*, the magazine of the College of American Pathologists, Lesko defended research on warfarin pharmacogenetics "conducted in a natural setting": "Many people feel that, when normal bias is controlled, prospective observational studies reflect more accurately how drugs are actually used…in terms of typical practice settings" (Lesko, cited in Check, 2009). This failure to take into account "real-world" conditions was a well-rehearsed problem with RCTs, and the same point was made by FDA's Janet Woodcock in a 2010 article:

> *A randomized trial…must, by ethical necessity, compare the results of genetic test-directed dosing with those of the highest attainable standard of care. This raises the issue of comparative effectiveness. Multiple studies have shown that, outside of trials and selected centers, individuals rarely receive INR monitoring that resembles this standard…(Woodcock, 2010, p. 770).*

However, this argument was unable to convince even those who saw the potential value of warfarin pharmacogenetics. In 2009, a large international study of warfarin dosing was reported in the *New England Journal of Medicine* (*NEJM*). The scale and geographical scope of this research collaboration was indicative of the level of scientific interest surrounding warfarin pharmacogenetics. The study involved 21 research groups from nine countries across four continents and was based on clinical and genetic data from 5,700 patients. The authors of this retrospective study concluded that a dosing algorithm using clinical and pharmacogenetic data

 

would have provided better outcomes for the 46% of patients who required a higher or lower dose of warfarin. However, the authors argued for further research: the pharmacogenetic dosing algorithm they had generated in their retrospective study should be tested in a prospective RCT (International Warfarin Pharmacogenetics Consortium, 2009).

In an editorial accompanying the *NEJM* paper, Woodcock & Lesko (2009, p. 811) refuted this argument, suggesting that personalized medicine required a fundamental epistemological shift in order to address questions which traditional RCTs were not designed to answer:

> *…although population-based, randomized, controlled trials of drugs control for disease variability, they generally do not reveal why some people do not have a response to treatment, others have excessive pharmacologic responses, and still others have side effects that occur in a distinctive pattern for a given drug.*

They concluded by returning to the problematic Lesko had set out in 2003 at the April meeting of the CPS – given the paucity of RCTs on marketed drugs then "clear thinking" was needed about the type of evidence demanded to support the adoption of pharmacogenetic testing. FDA officials were communicating two rather different messages: one was that RCTs were highly desirable but not necessarily feasible; the other was that RCTs were no longer the gold standard. The latter position had already been outlined in the 2006 Critical Path Opportunities Report. Acting FDA Commissioner Lester Crawford stated that RCTs were crude, mere "*trial and error* empirical testing"; the data which the agency wanted to encourage greater use of was "more mechanistic approaches built on new molecular and genomic knowledge" (Crawford, 2006). The epistemological shift advocated by Lesko and Woodcock was not simply from RCT to observational study; it was the combination of mechanistic data about the genomic basis of drug action and observational clinical evidence that was presented as superior to RCTs.

The following year in 2010, the most senior members of the US genomics science community joined the debate about what constituted suitable evidence for personalized medicine. Francis Collins, now head of NIH and formerly director of the Human Genome Project, and two colleagues, reasserted the primacy of the RCT, calling for "well-designed prospective clinical trials that measure patient-oriented outcomes," as a response to what they termed the "inherent, unresolved tension between genomics-enabled personalized medicine and the tenets of population-based, evidence-based medicine" (Feero *et al*., 2010, p. 2010). A few months later the protocol for such a study was published: the COAG trial, a double-blind RCT to compare clinical and pharmacogenetic dosing algorithms in warfarin patients (French *et al*., 2010).

But FDA had already made a further update to the warfarin label in January 2010. Drawing on the Medco/Mayo study, the label was updated to include genotype-based dosing ranges, a move toward the kind of detailed dosage guidance, which had been absent at the 2007 label revision. However, the 2010 relabeling still lacked a recommendation to perform pharmacogenetic testing. Perhaps for that reason, and in contrast to the media promotion of the initial 2007 label revision, the 2010 update was accompanied by neither a press conference nor even a press release. FDA subsequently justified their action in a special issue of *Clinical Pharmacology and Therapeutics* devoted to the question of clinical utility in pharmacogenomics. Lesko and two FDA colleagues were guest editors for the special issue, which provided the agency with the opportunity to reframe the warfarin pharmacogenetics debate, shifting it away from the morass of disagreements about individual data points to the more elevated terrain of general principles. This attempt to achieve closure was exemplified by Janet Woodcock's concluding comments in her contribution to the issue:

> *The controversy over clinical utility of diagnostics in drug therapy is a reflection of the underlying progress in understanding the basis of variability in human responses to interventions; in this regard, it is good news. Most scientific progress is ushered in by disputes and disagreements, hopefully, these will not cause us to lose sight of the promise of safer, more effective drugs in the near future (Woodcock, 2010, p. 773).*

Woodcock reframed past action in the context of future promise. Controversy about the warfarin relabeling was not evidence of a tactical error by FDA, but a vindication of its strategic vision, a necessary corollary of the progress it was making in realizing the promise of personalized medicine.

 

## 5. Discussion

"Pharmacogenetics is dead and warfarin killed it" *US industry executive, interview, 2011*

FDA was stretched on multiple fronts in the warfarin controversy, testing the limits of its power and authority. It was seeking to transform the scientific basis of its authority by constructing a new regulatory epistemology, while asserting a new role for itself as an enabler of innovation. It was trying to act in the postmarket environment, a regulatory space in which it has traditionally had limited influence, the legitimacy of its actions constrained by the principle that it does not govern medical practice, and its new regulatory epistemology questioned by an array of other actors with their own gatekeeping functions. Enacting promissory regulation through its relabeling project, the FDA shifted from grand vision statements to the prosaics of regulatory decisionmaking. As its advocacy for genomic science translated into the promotion of specific technological applications, the Agency found itself in a liminal space between the regimes of hope and truth, struggling to balance the ratio of vision and data.

Through its relabeling project, FDA sought not simply to inform clinical practice but to transform it. Senior agency officials envisaged a future in which doctors would routinely use pharmacogenetic tests to guide treatment decisions, and they used the drug label as a mechanism to realize their vision. The metric of success for FDA's relabeling project was therefore clinical adoption of pharmacogenetic testing; this rested on a significant expansion in FDA's reach and power in the postmarket space, testing its capacity to govern clinical practice. This was fiercely resisted. Whatever the progress of FDA's broader vision for personalized medicine, warfarin pharmacogenetics failed as a useful vehicle for clinical translation. New evidence has accumulated but large RCTs published in recent years have provided mixed evidence; warfarin pharmacogenetics continues to be deemed investigational by health care payors and it has neither been endorsed in clinical guidelines (Haga & Kantor, 2018).

### 5.1. Promissory regulation

The FDA's relabeling project, exemplified by the warfarin case, was a form of promissory regulation. FDA leveraged its position as a market intermediary, to function as a promissory organization helping to build a market for pharmacogenetic tests. The information it offered to clinicians and the encouragement it gave to diagnostics firms were performative of a particular sociotechnical future: a new era of personalized medicine based on genomic science. The future-oriented nature of promissory regulation helps to explain FDA's willingness to act in anticipation of more positive data, rather than to wait for it; an approach consistent with broader deregulatory trends in the era of permissive pharmaceutical regulation. However, although permissive regulation and promissory regulation are linked, they are not the same. Permissive regulation is a form of deregulation, it is about minimizing regulatory restrictions on the marketing of new drugs; promissory regulation is better understood as a form of *re*regulation that combines the creation of a new genomic regulatory science with efforts to build a clinical market for genomic technologies.

FDA's advocacy was consistent with its new role as an enabler of innovation, but it engendered concern about potential conflict with its gatekeeping role. Moreover, its decision to very publicly promote warfarin as a poster child for pharmacogenetics increased public visibility and professional scrutiny. The warfarin relabeling controversy is an example of the clash of two regimes in biomedicine: the regime of hope and the regime of truth. Moreira and Palladino (2005) suggested that agencies like FDA are rooted in the regime of truth: it is the promoters of new technologies – scientists, patient groups and firms – who construct the regime of hope. The relabeling project positioned FDA in a liminal space between the regimes of hope and truth; the agency recalibrated the ratio of vision to data as it promoted pharmacogenetic testing as a new technological paradigm.

What one pharmacogenetics researcher described in 2006 as "fuzzy labels" are central to the warfarin controversy and to the tension between vision/hope and data/truth. Promissory organizations offer fuzzy visions, but drug labels communicate hard data. FDA's entrepreneurial function as an enabler of innovation impelled it to relabel drugs to include pharmacogenetic data, but the agency's regulatory function required that it be circumspect in relabeling – it added pharmacogenetic data but it did not mandate pharmacogenetic testing as a condition of treatment or dosage decisions. FDA's relabeling strategy has reflected the need to manage the tension

 

between vision and data, rarely moving from a mechanistic epistemology (we know these genes influence drug metabolism) to a clinical logic (here is how to use genetic data in medical practice).

### 5.2. Postmarket power and regulatory epistemologies

In seeking to understand the conflict between FDA and postmarket gatekeepers, we might extend the concepts of fuzziness and liminality and suggest that they are intrinsic to drug labeling as a regulatory practice. The crafting of drug labels is a significant part of the premarket approval process, but the label extends FDA's influence into the postmarket space as means for the agency to guide physicians in the appropriate use of drugs. The label thus straddles premarket and postmarket space in a liminal position between the regulation of medical products by FDA and the regulation of medical practice by physicians. The relabeling project involved an attempt to increase FDA power over postmarket space, but other actors resisted this incursion into their territory. To evoke Carpenter's model, just as FDA's conceptual power to shape drug development standards is founded on its gatekeeping power to control market entry, so too actors in the postmarket space leveraged their function as gatekeepers to the clinic and asserted their own conceptual power, insisting on a different regulatory standard. This story thus illustrates the continued weakness of FDA in the polycentric space of postmarket regulation, and the limits of the drug label as a mechanism to shape clinical practice.

FDA could not bypass the gatekeepers controlling access to the clinic and the ensuing postmarket power struggle was a contest for the legitimacy of rival regulatory epistemologies. In their advocacy for pharmacogenetic testing, senior FDA officials increasingly expressed a preference for 'real world' observational data when it was underpinned by evidence about the molecular basis of drug metabolism over what it termed the "trial and error empirical testing" regime of RCTs. Sceptics, by contrast, argued for large-scale RCTs as the only credible basis on which to change clinical practice.

How then might we best understand the failure of FDA to extend its authority by establishing a new regulatory epistemology? Firstly, it is important to note that no one disagreed with the central tenet of pharmacogenetics – evidence demonstrating the genetic components of interindividual variation in response to warfarin. By the established standards that guide these decisions, the data were sufficiently compeling to justify updating the warfarin label. Furthermore, FDA's promotion of a new mode of genetic testing without evidence of improved clinical outcomes generated by RCTs was consistent with how the agency generally regulates diagnostic devices – it requires evidence of clinical validity (that the biomarker is predictive of a particular disease state or physiological function) but not clinical utility (i.e. improved clinical outcomes). FDA commonly accepts clinical evidence about diagnostic tests from studies that are less rigorous than RCTs, and such evidence has often been sufficient to gain coverage from payors and endorsement in clinical guidelines.

However, in recent decades, a variety of what we might term *diagnostic reformers* drawing on the principles of EBM have demanded greater rigor in the clinical validation of new diagnostics, and a succession of policy reports has called for increased oversight and greater attention to the evaluation of clinical effectiveness of genetic tests. Our case exemplifies these higher evidentiary expectations. Even the FDA has not abandoned the RCT, which remains the evidentiary gold standard for the approval of most new drugs and thus an integral component of the agency's scientific authority. As argued by Demortain (2017), in regulatory science standards "resist change."

## 6. Conclusion

What is the broader significance of this story? A growing body of scholarship advocates for new forms of *anticipatory* regulation (Armstrong & Rae, 2017) or *tentative* governance (Kuhlmann *et al.*, 2019) to address emergent science and technologies. Our case offers two key lessons. Firstly, that there are legitimacy threats for regulators if they become too identified with specific technological options. Secondly, that in polycentric regulatory regimes the most complex policy challenge may not be balancing the demands of industry and the concerns of the public, but negotiating between different regulatory actors.

The warfarin controversy can be understood as reflecting important tensions that arise from two distinct modes of risk governance that are captured in Majone's model of the regulatory state and Mazucatto's model of

 

the entrepreneurial state (Majone, 1997; Mazzucato, 2014). The FDA is most powerful agency of the US regulatory state, and in the era of permissive regulation, it has increasingly operated through risk management. However, when it took on a new role as an enabler of innovation, it was functioning as part of the entrepreneurial state with a much greater emphasis on risk-taking. The entrepreneurial state manifests the continued belief that technological innovation is central to economic growth, and that the promise of knowledge-based postindustrial capitalism requires an activist state that invests in cutting-edge technologies. Here, the role of the state is to build new markets by taking risks where industry is unwilling to invest, precisely the role that FDA took on when it relabeled warfarin in response to strong signals from molecular diagnostics firms that they would not invest in pharmacogenetic testing without FDA support for this new market.

We hesitate to characterize this market-building role as an instance of regulatory capture, although there is some explanatory value in the concept of "cognitive capture" - that FDA was adapting to cutting-edge trends in industry (Johnson & Kwak, 2010). However, since the genomic turn was pervasive across biomedical research, in academia as well as industry, then even cognitive capture is an inadequate term, given that it privileges the interests and actions of industry. Browne's (2020) concept of regulatory gifting, with its model of deregulation in cause of a broader public good, has greater value, but in this instance, as argued earlier, we think promissory regulation may encompass both deregulation and reregulation. However, as with Browne's UK example, regulatory policy is being driven by concerns about economic growth: FDA's advocacy for genomics was not simply a response to the perceived needs of industry, but to the broad and powerful commitment by the US state to promote genomic science (and biotechnology more generally) as part of an economic strategy to secure and maintain global leadership in the knowledge-based economy (Hogarth, 2015). From this perspective, promissory regulation may be understood as an exemplar of what Levi-Faur (1998) has described as the neo-mercantilist nature of contemporary regulatory capitalism.

## Acknowledgments

Research funding came from the European Commission Framework Programme Six HTA-methodology for innovative healthcare technologies (Inno-HTA), grant agreement 44390, and from a consultancy project for Health Canada. The paper was presented at *Towards personalised medicine? Biomarkers in practice* conference at University of Vienna and to a seminar at the Department of Global Health and Social Medicine, King's College London. The authors thank David Levi-Faur for editorial guidance; the three anonymous reviewers, Courtney Davis and Alberto Gutierrez for their detailed comments on drafts of the paper; and Olga Loblova for editorial assistance.

## Conflict of Interest

The authors have no conflicts of interest.

## Endnotes

[1] Clinical studies may be either observational or experimental. In experimental studies, the presence or absence of undergoing an intervention defines the groups, whereas in observational studies, the investigator does not intervene and rather simply "observes" and assesses the strength of the relationship between an exposure and disease variable. Experimental studies, or controlled clinical trials, involve one or more interventions, at least one control intervention, specified outcome measures for evaluating the studied intervention, and a bias-free method for assigning patients to the intervention. Trials are classed as RCTs when mathematical techniques are used to assign patients to test or control treatments. An explanatory trial is aims for causal understanding by testing hypotheses, and thus requires the strict control over experimental conditions, using sophisticated matching and exclusion techniques to ensure group homogeneity. A pragmatic RCT aims to estimate and compare the effects of clinical interventions in "real-world" settings, using simpler randomization procedures and relying on large-scale studies to address confounding. Observational study designs include case–control, cohort, and cross-sectional. Case–control and cohort studies measure disease occurrence and correlation upon given exposure including a prospective or retrospective temporal dimension. Cross-sectional/prevalence studies examine disease/exposure at one point in time.

 

[2] Woodcock had been Director of Center for Drug Evaluation and Research (CDER) from 1994 to 2005 and then from 2008 until the present.

[3] Definition provided at https://www.bcidaho.com/providers/medical_policies/mp-definitions.asp

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