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The ratio of vision to data: promoting pharmacogenetics through promissory regulation in the USA

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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), quoted in 1998.[1]

> "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, 2009[2]

In each of these quotes officials of the US Food and Drugs Adminstration (FDA) discuss the potential for genomic science to transform drug development and medical practice. Little over a decade separates the two statements, yet the ideological distance between them seems rather greater than the temporal gap. The comment from Jerry Collins is drawn from a feature in Nature Biotechnology in 1998. The article reported that the FDA (and the world's other leading pharmaceutical regulatory agencies) had limited interest in how new forms of genomic data might be used in drug approval. Yet the latter quote from the current (2015) Commissioner of the FDA exemplifies how that sceptical disinterest turned to evangelical zeal in just a few years; there had been a recalibration of what Jerry Collins referred to as "the ratio of vision to data". In this paper we characterize that recalibration as an instance of promissory regulation.

Others have described how the clinical and commercial expectations surrounding genomic technologies constitute a nascent bioeconomy of hope fuelled by promissory visions of a transformation of clinical practice, improvements in human health and economic growth.[3] Less noted is the fact that by 2004 regulators had added their voices to the chorus of academic scientists and industry executives who were engaged in the visionary promotion of genomic science. Both the FDA and the European Medicines Agency (EMA) were presenting pharmacogenetics as a crucial component in their plans for a fundamental re-engineering of the pharmaceutical R&D process. This championing of socio-technical futures, we argue, exemplifies a broader shift in the organisational identities of pharmaceutical regulators: their traditional role as guardians of public health has not been relinquished but it has been supplemented by a new role as enablers of innovation.

Although this techno-enthusiasm was a transatlantic phenomenon shared by both EMA and FDA, this paper focuses on the US story, exploring the FDA's new-found enthusiasm for pharmacogenetics and the reception of that enthusiasm by other actors in the regulatory space. Our account centres on what has been a key manifestation of this regulatory activism in the USA: the relabeling of approved drugs to include data on how pharmacogenetics influences inter-individual variation in drug response, affecting both safety and efficacy. Gathering such data and communicating it to doctors and patients via the labels of approved drugs has been a central part of the FDA's strategy for the promotion of pharmacogenetics and is described hereafter as the FDA's relabeling project. If the goal of that project had been simply to provide more information to doctors and patients about the genetic dimension of drug safety and efficacy, then its success might have been measured by the number of drugs relabeled, but the FDA had a grander ambition: it sought not simply to inform clinical practice but to transform it . The FDA envisaged a socio-technical future in which doctors would routinely use pharmacogenetic tests to guide treatment decisions. The metric of success for the FDA's PGx relabeling project was thus clinical adoption of pharmacogenetic testing. Measured by this criterion, the project has been a failure.

In seeking to describe and explain that failure, we take as our frame of reference a pivotal period in the early history of personalised medicine - the years between 2004 and 2009 - and describe how the FDA's strong advocacy for pharmacogenetics failed to translate into a revolution in clinical practice, despite scientific support amongst the biomedical research community, the commercial might of the world's leading diagnostics company and the political support of the US Health Secretary. This failure is attributed in part to clinical resistance, and in part to the scepticism of healthcare payors and health technology assessment (HTA) agencies.

The paradigmatic application which we focus on is pharmacogenetic testing for the CYP450 genes. Given that the role of these genes is well-established and that they have an impact on a significant proportion of the existing pharmacopeia, it is perhaps unsurprising that many believed that CYP450 testing could become the poster child for pharmacogenetics. Our narrative begins in 2004 with the first FDA approval of a test for the CYP450 genes (the Roche Amplichip) and its subsequently rejection in a series of Health Technology Assessment reports which all cited a lack of evidence for the clinical utility of testing. In the midst of this failure advocates of pharmacogenetics searched for a compelling application of CYP450 testing which would answer the sceptics, and much hope became focused on the blood-thinning drug warfarin. The FDA's relabeling of warfarin in 2007 was hailed by senior figures in the agency as a proof of concept for personalised medicine but this decision generated further controversy, amplifying, rather than resolving, differences of opinion concerning the weight of evidence and types of evidence required to support the adoption of pharmacogenetic testing. We show how this controversy came to centre on what has been a cornerstone of the modern pharmaceutical regulatory regime: the randomised control trial

(RCT). We describe how PGx advocates in the FDA sought to question the value of the RCT, an institution whose epistemological primacy is in large part an achievement of the FDA, and how the RCT was defended by other actors.

Our account allows us to explore the relationship between regulation and innovation in the social construction of new biotechnologies. What does it mean for a data-dependent organisation to become a visionary one, when its reputation rests on rigorous evaluation of scientific evidence? How do regulators manage the tension between vision and data as they renegotiate their role in the post-genomic era? This tension between the FDA, professional societies and HTA agencies leads to our final research questions: what can our study reveal about the increasingly complex nature of the pharmaceutical regulatory regime?

Background and conceptual framework

Our conceptual framework brings together multiple strands of work: on how regulatory practice and policy is developed through regulatory experiments; on the nature of regulatory power in the domain of pharmaceutical innovation; and on the role of expectations in the development of new sociotechnical regimes.

Regulatory experiments

Two recent accounts of the history of pharmaceutical regulation in the USA suggest that the defining principles of the regulatory system have emerged not through a top-down process of legislative dictat, but bottom-up from the daily practice of regulation. The 1962 Kefauver Amendments to the FDCA are traditionally the focal point of narratives which chronicle the emergence of the modern pharmaceutical regulatory regime: the premarket review of drugs to evaluate their safety and effectiveness, the three-phase system of clinical trials, and the requirement for randomised control trials (RCTs). But in his comprehensive history of the FDA's role in US pharmaceutical regulation, Dan Carpenter describes how key aspects of the 1962 legislation - such as the RCT and the system of three-phases trial system - simply gave legislative authority to what FDA officials had already begun to do. Once enshrined in the 1962 legislation the FDA's new powers had to be further elaborated through implementation in practice over the next two decades. Empowered by Congress, the role of FDA officials was to "formalize and give concrete meaning to a new regime of drug development and approval."[4] For instance, whilst the legislation required the sponsors of new drugs to demonstrate the safety and effectiveness of their products through "adequate and well-controlled investigations", it was FDA officials who gave definition to this requirement, giving primacy to "placebo comparison in well-designed double-blind clinical studies".[5] Carpenter characterises this process as "an ambiguous equilibrium of practice and meaning, an equilibrium sketched out slowly in regulatory experience."[6]

Donna Messner's account of the development of new modes of accelerated drug approval in the in the 1980s and 1990s, described how the established regulatory regime came under challenge.

Like Carpenter she describes a process of bottom-up reform in which agency officials exploited the latitude afforded them by regulatory ambiguity in order to adapt existing rules to new circumstances.[7]

The work of Messner and Carpenter provide two insights which are crucial to this paper. Firstly, Carpenter describes the dynamic interdependence between FDA officials and the biomedical research community. The modern regulatory regime depended on tools borrowed from biomedicine – such as the RCT and the system of three phases for drug trials. This structure of biomedical research gave the FDA's authority a mantle of scientific objectivity which was crucial to its legitimacy, and, in turn, the FDA's adoption of these tools amplified their importance, enshrining their crucial role in drug discovery and development. This feedback loop was a virtuous spiral of power, which we shall suggest, is being repeated as the FDA responds to the genomic turn in the life sciences by reshaping the rules of drug discovery and development to make it fit for a new era of personalised medicine.

Secondly, their accounts of the dynamic relationship between legislative change and bureaucratic autonomy demonstrate how this process of administrative bricolage is, in its ad hoc improvisational nature, inherently experimental. As Messner suggests: "Regulatory 'exceptions' were sometimes more like regulatory experiments for new rule-writing."[8] In previous work we have argued that the FDA and the EMA's approach to pharmacogenomics is emerging through a series of regulatory experiments, a concept drawn from the work of Millo and Lezaun:

> Regulators sometimes become experimenters: they try their ideas out before putting them into practice, test new policies in order to predict their consequences, or conduct trials and pilot programs to measure the effect of their plans before fully implementing them. Experimentation is a distinct and often crucial phase of the policy process, when regulators try to produce knowledge under controlled conditions, to assess the likely consequences of their actions before these become irreversible.[9]

Drawing on this model, we have described the creation of new pre-regulatory and pre-competitive spaces within which regulators, industry and scientists can experiment with the application of pharmacogenomics in drug regulation.[10] This picture is consistent with Millo and Lezaun's model that regulators sometimes conduct experiments in controlled settings to test new policies prior to implementation in the real world. They contrast their model with previous work which has focused on the quotidian practical application of regulatory science as a real world endeavour, a type of "normal science" which lacks any innovative edge.

The model of a clear distinction between policy development in controlled-world experiment and policy implementation in real-world practice fits well with the cases discussed by Millo and Lezaun but it does not seem to chime with the model of pharmaceutical regulation offered by

Carpenter and Messner. In their model policy emerges through real-world experiments conducted on the regulatory shop-floor, rather than trickling down from an ivory tower. Similarly, in our previous work we have described pharmacogenomics becoming regulatory science not only through trials in controlled settings, but also the through the extension of the experimental mode into regulatory practice. In particular, we argued that for the FDA the relabeling of approved drugs to include pharmacogenetic data was "a real-world regulatory experiment, a process of trial and error in which the drug label itself had become an experimental space."[11] In this paper we focus in more detail on what we term the FDA's PGx relabeling project, arguing that it was an experiment which generated profound controversy amongst other actors in the regulatory space. In seeking to make sense of this discord we draw on the well-established STS approach which deems scientific controversies valuable because they bring into stark relief the social relations which constitute scientific work. In this case the social relations we wish to explore are those which constitute the emergent sociotechnical regime for personalised medicine and the regulatory space of pharmaceuticals in the USA.

Regulatory power

Before outlining the complexity of the regulatory space, we shall outline a model of regulatory power which draws on Dan Carpenter's history of the FDA. Carpenter provides a taxonomy of the FDA's regulatory power comprising three facets – directive, gatekeeping and conceptual. *Directive* power is the exercise of legal authority by the regulator over the regulated subject – in pharmaceuticals it may take the form of an instruction to add a warning about adverse events to a drug label or to change a manufacturing process. The FDA's *conceptual* power is its influence in shaping "the basic terms, standards, schedules and rules of modern drug development."[12] However, it is the FDA's *gatekeeping* role which Carpenter sees as the fulcrum of agency's authority, the wellspring which "sustains a battery of vast powers"[13] *Gatekeeping* power is the agency's control over market entry, the fact that "FDA approval is the only route to market for a new drug."[14] Whilst the FDA's role as gatekeeper is enshrined in statute, the effects of gatekeeping power do not always require the formal exercise of legal authority; it is often the shadow of that authority: the broad direction of corporate R&D strategy and minutiae of decisions about individual products are shaped by assumptions about how the regulator might respond.

The centrality of gatekeeping to the power of the FDA sets the spatial and temporal limits of its authority, which are mainly in the premarket phase. Once a drug has received market approval the agency's authority is far more restricted, a weakness exemplified by its inability to enforce completion of postmarket studies which it has asked manufacturers to conduct.[15] The FDA has a variety of regulatory implements in its postmarket toolbox such as manufacturing and packaging revisions, but it has increasingly come to rely on relabeling as the principal means of addressing post-approval issues. Yet, a 1997 survey revealed that 85% of US doctors stated that FDA labels have "little" or "practically no influence" on their treatment decisions.[16] This postmarket weakness is a central part of our story.

However, it would be wrong to characterise the postmarket space as a regulatory vacuum. Whilst most work on pharmaceutical regulation focuses on the role of statutory licensing agencies like the FDA, the postmarket environment is a complex regulatory space occupied by multiple gatekeepers who have some influence over how a new drug moves into routine clinical practice. The statutory licensing authority is responsible for evaluating safety and effectiveness, but healthcare payors, HTA agencies and professional bodies, have an interest in issues of cost, comparative effectiveness and how new treatments and technologies might fit into existing clinical pathways. Companies must convince healthcare payors to pay for their products and clinicians to adopt them, and these gatekeepers frequently carry out their own evidence reviews in order to make decisions or recommendations which are then enshrined in HTA reports, coverage decisions and clinical practice guidelines.

The regulatory space has become more complex over time. For instance, the Health Technology Assessment (HTA) movement emerged in the 1970s from a concern that new medical technologies were entering clinical practice fuelled by optimistic and often unquestioning acceptance rather than formal evaluation of evidence. HTA was a new knowledge production process which utilised the healthcare system as "... a research laboratory for the field-testing of the effectiveness and cost-effectiveness of healthcare technologies."[17] Rising healthcare costs were a significant factor in this development, but not the only one; the period also saw the development of a critique of high-tech medicine which questioned "both the quality and the very aspirations of health care."[18] HTA can thus be understood as part of a broader trend towards technological scepticism in the biomedical arena and a desire to slow down, or at least control more carefully, the innovation process in healthcare.

Equally significant have been the emergence of evidence-based medicine (EBM) and the growing importance of clinical practice guidelines as a means to improve healthcare by the systematic evaluation of scientific evidence. In the USA 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."[19] Timmermans and Berg have described how this trend grew rapidly from the late 1980s and suggest that its increasing importance was in part a defensive manoeuvre by the medical professions to retain their authority - if EBM's assault on the autonomy of the individual physician could not be halted, then professional influence could be defended by establishing the collective role of professional societies as promulgators of guidelines.

There is thus a profound temporal and spatial bifurcation in the operation of power within the pharmaceutical regulatory regime. In the premarket space regulatory power accords with a traditional model of command-and-control regulation in which the sovereignty of the regulatory agency over the regulated industry is paramount, but in the postmarket space

power is much more diffuse: not only is the balance of power between regulator and industry more equal but the role of gatekeeper is shared amongst multiple actors.

Promissory regulation

Regulators have a crucial role to play in the shaping of new biotechnologies. Regulatory agencies have been theorised in a number of ways within political science and science and technology studies (STS) with the main emphasis placed on their role in governing innovation.[20] This role has multiple dimensions, including the need to address commercial uncertainties about the regulatory path to market, and the need to build public and professional trust in new technologies. However, Abraham and Davis suggest that STS scholars need to pay more attention to regulators' role in promoting certain visions and expectations of new technologies; an important aspect of the sociotechnical shaping of artefacts and practices.[21]

How might we conceptualise the adoption of such a role by regulators? Here we draw on Pollock and Williams (2010) suggestion that *intermediaries* can play a pivotal role in shaping the expectations and articulating the visions which help to constitute emergent technologies, a role which they describe as the "promissory organisation".

> Promissory organizations are defined as intermediaries, which are prodigious in the production of future-oriented research that not only represents the state of affairs in a particular marketplace but also contributes to shaping such markets. Our specific aim is to understand the extent to which their advice is 'performative' – suggesting that technological visions mobilized in the building of technological fields do not simply describe future technologies but also help to bring them into being.[22]

Pollock and Williams focus on the role of industry analysts in the IT industry, but in this paper we focus on the critical role of regulators, exploring how the FDA used its conceptual power and role as gatekeeper to gain a critical position in articulating future visions about personalised medicine in the USA.

In seeking to understand how regulators manage the tension between vision and data, we draw on Abraham and Davis' argument that the regulatory arena is one in which there may be conflicting expectations - "hopes" and "promises" might conflict with the regulatory demand for standards and evidence. They suggest that "the interests and expectations of different groups become linked in the institutional and professional networks of drug regulation" and that in certain circumstances promissory science may have a negative impact on regulatory precaution. In a recent paper Brown and Benyon-Jones have written on the pervasive perils of promissory policymaking in biotechnology:

> Periods of technological hype are typically followed by periods of disappointment and crises of legitimacy. This can impact disproportionately upon the more vulnerable actors ...

> [such as] policy actors (regulators, government, funders) who are often disproportionately susceptible to positive promotional persuasion and lobbying about the developments which they seek to regulate. To this extent, policy-making can often bear significant responsibility for inflaming successive cycles of hype and disappointment.[23]

In this paper we suggest that the FDA's relabeling project, and the warfarin case in particular, exemplifies the perils of promissory regulation.

Pharmacogenetics: promise and controversy 2003-2007

In April 2003 when the complete sequencing of the human genome was announced the US Secretary for Health and Human Services Tommy Thompson described the achievement as "momentous ... the dawn of a new era in medicine and biology."[24] In the same month the FDA Commissioner Mark McClellan wrote of the promise of pharmacogenetics: "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"[25] A few days later a new FDA advisory committee considered how to operationalize pharmacogenetic testing in clinical practice.

The Clinical Pharmacology Subcommittee of the FDA was an offshoot of the Advisory Committee for Pharmaceutical Science and had been established the previous year. Among its members were two of the USA's leading experts on pharmacogenetics: Howard Macleod of the University of North Carolina and David Flockhart of Indiana School of Medicine. This new committee would become an important forum for discussion of the FDA's relabeling project. Setting out the agenda for the April 2003 meeting was Larry Lesko, Director of the Office of Clinical Pharmacology and Biopharmaceuticals (OCPB) and one of FDA's most prominent advocates for pharmacogenetics. Lesko described pharmacogenetics as "a work in progress" but one which the FDA was keen to exploit as part of a broader initiative to improve drug safety:

> "where we're heading is to create a general construct for looking at improvement in existing therapies … approved drugs, to determine what criteria we ought be thinking about that would warrant updating labels for products to optimise drug dosing using genetic information."[26]

On the second day of the April 2003 meeting Lesko described how this topic was already generating controversy:

> "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."[27]

He suggested that prospective clinical trials might be a challenge, since it was unclear who would conduct the research, and so other forms of evidence such as systematic reviews of academic studies or expert opinions from professional groups might have to be relied upon. This debate about the type of evidence and amount of data required to support pharmacogenetic drug relabeling and clinical adoption of pharmacogenetic testing was to become a major stumbling block for FDA's evolving vision for personalised medicine.

In 2003 the FDA relabeled the cancer drug 6-mercaptopurine thiopurine drugs to indicate the increased risk of adverse events as a result of inter-individual variation in TPMT activity. In 2006 another cancer drug, Irinotecan, was relabeled, again to warn of safety risks, this time associated with the UGT1A1 gene. However, in neither case did FDA relabeling make a major impact on clinical adoption of pharmacogenetic testing. Laboratory directors, a key group for the successful adoption of new diagnostic tests, complained that the pharmacogenetic data on drug labels was insufficient to guide dosing decisions and that the absence of clear guidance raised concerns about liability. These issues were made clear by the leading molecular pathologist Debra Leonard 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 labeling 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.[28]

The HTA community were 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 of routine reduction of initial irinotecan dose in *28 homozygotes based on UGT1A1 genotyping is unknown. No study has prospectively documented the potential benefits (reduced adverse drug events) or harms (reduced proportion of responsive tumors).[29]

The EGAPP review was published in 2009 but clinical resistance and HTA scepticism was already a well-established response to efforts to introduce pharmacogenetic testing, whether promoted by the FDA or the molecular diagnostics industry. This wariness was exemplified by responses to FDA approval of the first microarray technology for pharmacogenetic testing.

The Roche Amplichip – an array of problems

In 2004 much excitement surrounded the Roche CYP450 Amplichip. The Amplichip was the first FDA-approved CYP450 test and the first pharmacogenetic microarray test to gain FDA approval. Produced by Affymetrix, then the leading microarray manufacturer, and licensed to Roche, who

claimed leadership of the IVD industry, the Amplichip combined state-of-the art genomic technology with pharmacogenetic content whose application was potentially very broad.

The clinical implications of the CYP450 genes were first demonstrated in 1978. A significant proportion of the most commonly prescribed drugs are metabolized by the action of cytochrome P450 enzymes which act in the liver to break down a variety of chemicals. Depending on the P450 genetic polymorphism carried, patients may be poor metabolisers, resulting in reduced drug effectiveness, or rapid metabolisers, who may be at increased risk of toxicity. An industry report pointed to the potential market value of CYP450 testing based on the breadth of its possible applications.[30] A 2004 review article by Kirchheiner et al looked at the potential to move CYP450 pharmacogenetics out of the laboratory and into clinical decision-making. [31] The authors expressed a widespread view that CYP450 was the pharmacogenetic application with greatest potential for early adoption in the clinic, but they sounded a note of caution about the need for greater data:

> ... in **clinical practice** the correlation between drug exposure and effect are modulated by **multiple other factors**. Thus, before routine genotype-guided dosing recommendations can be made for patients, future studies ... need to be completed, especially **prospective** studies evaluating such genotype-guided dosing strategies. [our emphases][32]

This, it would transpire, was a prophetic vision of the significant challenges facing those who sought to promote the adoption of CYP450 testing in the clinic, not least Roche Molecular. In the United States their Amplichip test was taken up by LabCorp, the country's second largest reference lab (as well as a number of smaller commercial laboratories) and was therefore widely available across the country. However, the test was not cheap, costing around $400, and one reference laboratory executive complained that it was "wildly overpriced". [33] The cost of the test turned out to be one of a number of issues which hampered clinical adoption of the technology.

Perhaps the most significant challenge to the Roche Amplichip came from HTA agencies. Despite FDA approval, a succession of negative HTA reports found insufficient evidence of clinical utility to support the use of the Amplichip to guide drug treatment. 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."[34]

At this stage even personalised medicine champions within FDA were expressing scepticism. At an industry conference in 2005 Larry Lesko suggested that the Amplichip had the potential to reduce adverse drug events by 20 percent but that its utility was still an "open question" and warning of the dangers of "genohyping".[35] His comment highlights the regulatory ambivalence

at the heart of FDA's pharmacogenomic relabeling project; the tensions arising from the agency's need to manage the ratio of vision to data.

Subsequent to the approval of the Amplichip it became clear that a range of other test manufacturers were prepared to launch rival kits, should there be significant clinical demand for the CYP450 testing, but it appeared that the availability of an FDA-approved test from the world's leading IVD company was insufficient to build a market for CYP450 testing, no matter how sophisticated the platform technology. Neither was the widespread scientific, commercial and political support driving the vision of a new era of personalised medicine of any great assistance. Some of Roche's commercial rivals suggested that what was needed was a killer app. Kari Parukkeri, CEO of the Finnish diagnostics company Jurilab, epitomised this view when he stated that a market would only develop if the FDA produced a mandatory relabeling recommendation, explicitly requiring the use of the test for a drug.[36]

Warfarin – poster child or problem child?

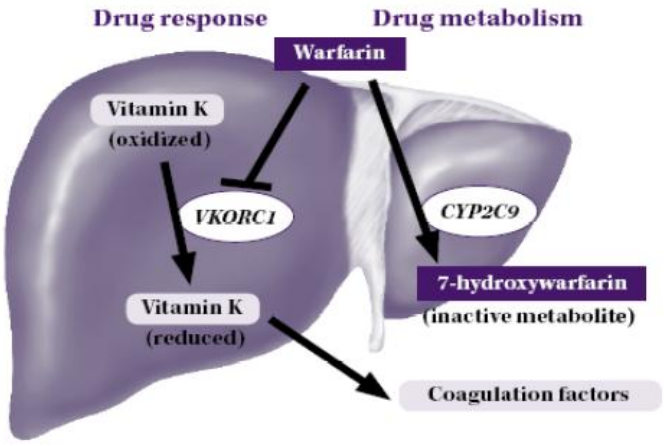
In November 2005 hopes of stronger pharmacogenetic relabelling guidance were raised when the FDA's Clinical Pharmacology Subcommittee voted to recommend that warfarin be relabelled to reflect the ability of genetic tests to guide dosing. There was unanimous agreement amongst the committee that there was sufficient evidence to recommend 1) that lower doses of warfarin be given to patients with genetic variations in the CYP2C9 / VKORC1 genes that lead to reduced activities; and, 2) that genotyping patients in the induction phase of warfarin therapy would reduce adverse events and improve achievement of stable INR in patients. There was an 8 to 2 majority in favour of relabelling to include genomic and testing information. A member of the panel anticipated that this would be the major breakthrough many were hoping for:

> "FDA-approved tests have very fuzzy labels … but the one for Warfarin will be a much stronger recommendation – the meeting was unanimous – when the FDA label change comes out in the summer it will be widely picked up."[37]

The potential impact on commercialisation is indicated by the response of Tm Bioscience, a Canadian diagnostics company poised to enter the CYP450 market. In its 2005 annual report the company announced that it was developing a warfarin test for market launch in 2006 and cited the relabeling recommendation as an example of how "The PGx market is being driven by several FDA initiatives."[38]

Why did so much hope come to rest on the relabelling of warfarin? The clinical and commercial case for genotype-based warfarin dosing has multiple dimensions: it is a widely prescribed drug and a leading cause of serious adverse events due to its narrow therapeutic index and wide inter-individual variability in dose requirements. Establishing the optimal dose for an individual patient can take weeks of careful monitoring using the Prothrombin Time test (PT) which evaluates the blood's ability to clot properly. Dosage is adjusted until the patient is at the same

value as found in healthy people, known as the International Normalized Ratio (INR). During this period there is a high risk of adverse events. The genetics of drug metabolism plays a major role in explaining inter-individual variability through the role of two genes: CYP2C9 and VKORC1. Warfarin is metabolised by CYP450 enzyme expressed by the CYP2C9 gene. Warfarin's anticoagulant effect is mediated by the enzyme VKORC1 – warfarin's target enzyme. Variation in CYP2C9 can cause slow metabolism, longer drug half-life, increasing blood concentrations of warfarin and greater anticoagulant effect. Variations in VKORC1 gene cause reduce enzyme activity and reduced function of coagulation. Taken together these can lead to increased risk of bleeding.



Source: AMA brochure

Kirchheiner's 2004 review article highlighted Warfarin's potential concluding that it was "most likely to be the first example of CYP2C9 genotyping in clinical practice."[39] A 2005 paper by Ann Daly confirmed the view: "The significant relationship between warfarin dose requirement and the CYP2C9 genotype is now one of the most frequently cited examples of a clinically relevant pharmacogenetic relationship."[40] Another UK scientist, Munir Pirmohamed, highlighted the broader significance of the Warfarin case:

> The importance of this lies not only in improving the use and safety of warfarin, but because it also serves as a paradigm for introducing pharmacogenetics into other therapeutic areas. [41]

By 2005 the weight of scientific data was sufficient to justify a systematic review and meta-analysis which confirmed the role of CYP2C9*2 and CYP2C9*3 alleles in warfarin metabolism and risk of bleeding and the potential role of PGx testing to inform clinical management. However, the authors concluded that "Evidence for the clinical utility and cost-effectiveness of genotyping is needed before routine testing can be recommended."[42] Kircheiner's paper had also highlighted the need for prospective data and Daly similarly concluded that more evidence

was needed: "the value of genotyping patients prior to treatment has not yet been rigorously assessed."[43]

The FDA responded to this call for more evidence in 2006 when the agency published a list of priority challenges which they sought to address by working in collaboration with academics and industry as part of its Critical Path initiative. The development of biomarkers for personalised medicine was one of these priorities, and the report singled out warfarin as an example of where pharmacogenetic testing could improve drug safety. However, the report acknowledged the need for rigorous dosing protocols based on the patient's genetic profile.

FDA relabels warfarin

The FDA's warfarin relabeling eventually came in August 2007, some 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 but did not give precise dosing recommendations. At the press conference to announce the decision were both Larry Lesko and Janet Woodcock, Deputy Commissioner and Chief Medical Officer of FDA.[44] 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. Janet Woodcock put it in the context of the Critical Path initiative: "So we're very pleased, I think, from the standpoint of the Critical Path that this is really a proof of concept."[45] Her boss, FDA Commissioner Andrew von Eschenbach, hailed the decision as "one step in our commitment to personalized medicine.[46]" But Woodcock also struck a note of caution, stressing that further research was ongoing as a Critical Path project:

> "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."[47]

Crucially, the FDA had not provided clear practical guidance on how to change patient treatment based on pharmacogenetic data, as Larry Lesko acknowledged in the FDA's press release: "Although genetic testing can currently identify who has these genetic variants, more studies are needed to explore the precise starting dose for these patients."[48] FDA, he explained, had been working to address this need in collaboration with the Critical Path Institute (CPI), an organisation established at arms length from FDA to broker public-private partnerships on Critical Path projects. An FDA-backed trial in collaboration with the healthcare providers Kaiser Permanente had not been completed and instead CPI was working with the University of Utah to develop guidance on PGx warfarin dosing, working with the National Heart, Lung and Blood Institute to support clinical trials on PGx-guided warfarin dosing and CPI was co-funding a clinical study being conducted by Harvard Partners.

At the press conference, Lesko also suggested that the FDA had some reservations about pushing testing too aggressively since physician access to the tests might still be limited. 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?[49]

Lesko defended their decision, arguing that they felt an obligation to share the data about the pharmacogenetics of warfarin with doctors and patients. However, the media's scepticism prefigured a wider disagreement with FDA's strategy.

Warfarin wars - clinical resistance and payor scepticism

FDA's decision to relabel warfarin amplified, rather than resolved, differences of opinion concerning the weight of evidence 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." It described the FDA's relabeling decision as "controversial", citing a number of other issues which compounded the lack of clear evidence and which weighed in favour of a continued focus on INR testing as the mechanism for individualizing dose adjustment:

> The tests cost $400 each. Waiting for the results might delay starting warfarin. The results can be confusing, as when one test suggests the need for a high dose of warfarin and the other indicates the need for a low dose. Some experts worry that doctors might rely too heavily on the genetic tests and not pay enough attention to the myriad other factors that influence how an individual responds to warfarin. Others are concerned that the new wording might prompt lawsuits from patients who do not have the test and later experience problems with warfarin.[50]

Pharamcogenetic testing, it concluded "may well be the wave of the future. For warfarin, right now, it's barely a ripple."[51] The scepticism is noteworthy, not only for its succinct summary of the key issues which would define the ensuing controversy, but because Harvard researchers were collaborating with FDA on the CROWN study to develop personalised warfarin dosing algorithms with support from the Critical Path Initiative. Further evidence of clinical scepticism came in 2008 when the American College of Chest Physicians published new anticoagulation management guidelines stating that: "[W]e suggest against pharmacogenetic-based dosing until randomized data indicate that it is beneficial (Grade 2C)". [52] A review of the evidence had been conducted by the American College of Medical Genetics in 2006 and its findings were published in 2008. It too highlighted the lack of utility data: "no study has yet shown this intervention to

be effective in reducing the incidence of high INR values, the time to stable INR, or the occurrence of serious bleeding events."[53]

Health care payors also weighed in to the controversy, most notably Blue Cross Blue Shield (BCBS), a major US healthcare insurer whose Technology Evaluation Center (TEC) is an influential part of the country's HTA community. BCBS TEC had already rejected the Roche Amplichip, and in 2008 they evaluated warfarin pharmacogenetics as 'investigational', a term used for health technologies which either have not gained FDA approval or have not demonstrated that they improve health outcomes.[54] 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 universal support, but, like other sceptics, they cited the lack of evidence demonstrating that pharmacogenetic testing could improve clinical outcomes.[55] Aetna came to a similar conclusion.[56]

Despite this controversy, warfarin testing attracted high-level political support. The US Health Secretary Mike Leavitt had launched an initiative on personalised medicine in 2007 and the following year he singled out the hopes attached to warfarin in the opening pages of his second report on personalised medicine, pointing to the hoped-for benefits: "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."[57]

A year after FDA's 2007 warfarin relabeling decision, the political significance of the label update was confirmed when the Center for Medicare and Medicaid Services (CMS, the branch of HHS responsible for federal healthcare delivery) launched a public consultation on whether it should cover warfarin testing for its patients. Responses to that consultation illustrate the divergence of opinion surrounding the issue: the American Association for Clinical Chemistry and the College of American Pathologists, two major national pathology professional bodies, were in favour but opposing coverage were two bodies representing clinicians: the American Heart Association and the American Society for Hematology, as well as the professional pathology group with greatest expertise in molecular diagnostics - 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: the agency agreed that previous studies had shown the predictive power of PGx testing for warfarin but stated that more data was needed. CMS softened the blow by ruling that warfarin PGx testing would be available to some CMS patients under the Coverage with Evidence Development programme, that is if patients were enrolled in a prospective RCT designed to compare pharmacogenomics-guided dosing strategies with standard dosing methods.

More evidence, more arguments

Amidst the calls for more studies, the evidence base was gradually accumulating, but this additional data did not lead to closure; rather it further entrenched the existing divisions, particularly around what type of data was acceptable.

The CoumaGen study was an RCT which had also been funded by the Critical Path Institute. Ray Woolsey, President of CPI, had described the warfarin study as "a first serious effort to prospectively, rather than retrospectively, develop and validate a pharmacogenomic method for treating patients"[58] Its results were published in 2007 soon after FDA's relabeling decision. [59] The paper found that the combination of pharmacogenetic and clinical factors provided an initial dose more closely predictive of the stable maintenance dose and thus entailed fewer and smaller dose adjustments and fewer INR measurements. However, the study did not achieve its primary end point: reducing out-of-range INRs. What the study suggested was that when doctors followed the traditional regime, adjusting dosage based on clinical data and PT testing, and when care was delivered to a high standard in a dedicated service, with patients initially kept in a hospital setting and monitored with daily PT measurements, then PGx data did not add that much value.

Given that this was a CPI-supported study, its findings are likely to have been a profound disappointment to PGx advocates in the FDA. Their response was indicative of how much political capital was now invested in the promotion of warfarin testing as an exemplar for personalised medicine. In 2008 the FDA's Larry Lesko and Brian Gage, a leading authority on warfarin PGx, published a paper rebutting the CoumaGen study findings. They argued that the study's results had been misreported in public comment with undue emphasis on its negative aspects, but they found multiple faults with the paper: not fully blinded, wrong endpoint, performance bias (due to frequency of PT testing), clinical arm of trial had greater number of patients with genotypes less likely to benefit from PGx. Lesko and Gage concluded by highlighting that more warfarin trials were underway, suggesting that it was only a matter of time before supportive data was forthcoming.[60]

One such study was a collaboration between the pharmacy benefits company Medco and researchers at the Mayo Clinic. This study was listed in the Critical Path Initiative report for 2009.[61] The genesis of this collaboration demonstrated the complex new networks which were being generated in the emergent socio-technical regime for pharmacogenomics. Felix Frueh, who had worked for Larry Lesko as associate director of genomics at FDA, left the agency for Medco in 2008 to run a new clinical research operation, whose primary focus was demonstrating the value of personalised medicine. The results of the Medco/Mayo study were published in 2010.[62] The study had two arms: genotyped patients and non-genotyped patients, and the hospitalisation 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 both criticising the study design, in particular the use of a historical control group which, it was suggested, may have introduced bias through cofounding. These critics highlighted that other trials which were currently underway were randomised and that the Medco/Mayo study could easily have been randomised too.[63] The authors of the paper responded that the lack of randomisation was not an oversight but a deliberate choice, defending their study as a conscious attempt to conduct research on how pharmacogenetics could improve warfarin dosing in *typical practice settings*, and contrasting their approach to that of the CoumaGen study.[64]

The warfarin PGx controversy had ceased to be about the need for *more* evidence; it was now a dispute about the *type* of data required, in particular about the value of the gold standard RCT. FDA officials like Larry Lesko were increasingly emphasising the value of retrospective/observational studies. Anticipating the publication of the Medco/May study in a 2009 feature in CAP Today, the magazine of the College of American Pathologists, Lesko defended warfarin PGx trials which were "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.[65]

The same point was made by 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 (because prescribers fail to order the monitoring, or individuals fail to comply, or both).[66]

However, this failure to take into account "real-world" conditions was not the only justification that senior FDA officials gave for suggesting that the RCT was not fit for purpose for the new era of personalised medicine; a more fundamental epistemological shift was being promoted which sought 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.[67]

The agency's new thinking had already been outlined in 2006 in the Critical Path Opportunities Report. The 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."[68]

However, many of those active in the growing warfarin PGx research domain were unconvinced by this argument. In 2009 the findings from a new study of warfarin dosing were reported in the NEJM. The scale and geographical scope of this research collaboration was indicative of the level of scientific interest which the topic was attracting: the International Warfarin Pharmacogenetics Consortium comprised 21 research groups from nine countries across four continents and the study was based on clinical and genetic data from 5,700 patients. The authors of this restrospective study concluded that a dosing algorithm using clinical and pharmacogenetic data would provide better clinical outcomes for outliers, ie.. the 46% of patients who require a higher or lower dose of warfarin. However, despite the scale of their study the authors did not conclude that they had definitively demonstrated the value of warfarin PGx. Instead they suggested that the dosing algorithm which they had generated "provides a robust basis for a prospective clinical trial of the efficacy of genetically informed dose estimation for patients who require warfarin."[69]

In an editorial accompanying the paper, the FDA's Woodcock and Lesko took the opportunity to outline once again their own views on what sort of evidence was required. Responding to those who advocated trials to generate evidence on clinical outcomes, they put forward an alternative perspective

> Others feel that more limited data will be sufficient for drugs such as warfarin, since the pharmacodynamic end point is, after all, the entire basis of warfarin dosage.[70]

In advocating the use of biomarkers as surrogate endpoints they returned to the theme of real-world practice as the basis for PGx studies, since their justification for this approach was the established practice of using PT testing to measure when patients on warafrin have reached INR. 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. This was a regulatory rationale which proceeded from an assumption about the scarcity of postmarket data. The idea that the regulator might demand such data from industry, either drug manufacturers or molecular diagnostics companies, has been precluded from the discussion. Yet the following year, the most senior member of the genomics science community in the USA joined the debate about what constituted suitable evidence for PGx applications. Francis Collins (by then head of NIH, but formerly director of the Human Genome Project) and two colleagues called 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" .[71] A few months later the protocol for such a study was published, the COAG trial is a double blind, randomized clinical trial to compare clinical and pharmacogenetic dosing algorithms in warfarin patients.[72]

In the meantime in January 2010 the FDA made a further update to the warfarin label. Drawing on the Medco/Mayo study, the label's pharmacogenetic data was expanded to include a table describing expected doses for initial dosing ranges for patients based on genotypes (see figure 1).

Figure 1: excerpt from Warfarin drug label

Table 5: Range of Expected Therapeutic Warfarin Doses Based on CYP2C9 and VKORC1 Genotypes†

VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

†Ranges are derived from multiple published clinical studies. Other clinical factors (e.g., age, race, body weight, sex, concomitant medications, and comorbidities) are generally accounted for along with genotype in the ranges expressed in the Table. VKORC1 –1639 G→A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3 and *3/*3 may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen.

Unlike the 2007 labelling change, this update was accompanied by neither a press conference nor even a press release. However, justification for the FDA's policy came in a collection of papers published later that year in a special issue of Clinical Pharmacology and Therapeutics devoted to the question of clinical utility in pharmacogenomics, and guest edited by Lesko and two FDA colleagues. In this collection of paper the agency's most senior PGx advocates sought to reframe the warfarin debate, shifting it away from the morass of disagreements about individual data points to the more elevated terrain of general principles. This 'big picture' was an attempt to achieve closure by recalibrating the ratio of vision to data, a manoeuvre 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.[73]

Controversy about the warfarin relabeling was presented here not as a failure on the part of FDA to apply the necessary regulatory rigour to need for clinical data, but as a vindication of its vision, a necessary corollary of the progress it was making. CDER's Director sought to situate current disputes about evidence in the wider sweep of historical scientific progress, and implied that this progress might be impeded if data disputes blinded actors to the overarching goals of personalised medicine. In doing so, Woodcock sought to restate the primacy of the FDA's future vision of the promise of personalised medicine to deliver safer, more effective drugs. The manoeuvre is one familiar to other scientific controversies; Nik Brown has described its application by industry in the GMO debate:

> "The closed present tense of current and past truths had occluded the future open tense of potential and possibility. [Regaining control of the debate] ... would depend on laying claim to future-oriented abstractions rather than messy present-day squabbles."[74]

Discussion

> "… where regulators have difficulties in controlling access to and use of modern technologies, these difficulties are, if anything, exacerbated where regulators themselves turn to the technology as a regulatory instrument."[75]

> "Pharmacogenetics is dead and warfarin killed it"[76]

The FDA's relabeling project sought to align the institutional interests of the agency (who wanted to enhance and extend their authority) with the commercial interests of the molecular diagnostics industry (who wanted to build a market for their tests). To a very limited extent it worked, in so far as it has galvanised a number of diagnostics companies to gain FDA approval for warfarin pharmacogenetic tests. Despite only limited clinical uptake, for some actors warfarin remains a focal point for expectations around pharmacogenetics. Thus the CEO of Iverson Genetic Diagnostics described the potential value of the WARFARIN study launched in 2011:

> Our successful leadership on this study will enhance Iverson's standing and authority in the emerging market for genetics-based personalized medicine with both industry and governmental decision makers. This opportunity will also provide an advantage in securing new business and in expanding our portfolio of services around the world.[77]

Yet such optimism remains just that, a future-oriented vision of what might be. Despite the best efforts of senior FDA officials warfarin dosing based on pharmacogenetic data remains an aspiration, not a reality. In a previous paper we suggested that the FDA's relabeling project had turned the drug label into an experimental space.[78] The Warfarin relabeling was the pivotal moment in this project, and it has thus far been largely a failure. Woodcock's description of the 2007 relabelling as "a proof of concept" was prophetic. If one assumes that she used the term to suggest that this was mission accomplished, then subsequent events simply confirmed that proofs of concept need considerable reworking before they can be scaled up for real-world application.

The uncertainty principles

How do we best explain the FDA's failure to encourage the clinical adoption of pharmacogenetic testing for warfarin? It is perhaps best to restate those points on which all parties seemed willing to agree: warfarin is a major cause of serious adverse events; improving the safety of

warfarin patients is an important goal; inter-individual variation in dosing response has a significant genetic component; and clinical adoption of warfarin pharmacogenetic testing requires clear guidance in the form of dosing protocols.

Firstly, the division articulated two very different ways of *framing uncertainty*: those who supported the relabeling decision focused on the uncertainty about warfarin dosing under the current testing regime; the time it takes to reach a stable, safe dose using PT testing: the skeptics focused on the uncertainty about the benefits of pharmacogenetic testing.

Secondly, the relabeling decision indicated the FDA's greater appetite for *embracing uncertainty*; a readiness to give pharmacogenetics the benefit of the doubt, as opposed to a scepticism about its doubtful benefits. This point was made clear by Lesko at the advisory panel 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. " Larry Lesko, Clinical Pharmacology Subcommittee meeting November 2005

The previous year Janet Woodcock had, in similar vein, given a presentation in which she stated that "... biomarkers have to be used to be accepted."[79] In 2010, this experimental approach to regulatory science was being retrospectively presented as a form of trial and error empirical testing, precisely the mode of enquiry which it was now seeking to denigrate as it downplayed the importance of RCTs for pharmacogenetics:

> "Each label update has provided **a unique opportunity to better understand** the nuances of adding PGx to labels and the subsequent impact of label updates on adoption into clinical practice and diagnostic test reimbursement."[80]

The division between sceptics and advocates 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 PGx testing carried out as part of an RCT, some payors were willing to countenance a regulatory experiment. Their disagreement centered on how far to extend the space of regulatory experiment. Consistent with its stated preference for real world observational data, FDA advocated rapid and widespread adoption in routine clinical practice in a regulatory experiment that would encompass all new warfarin patients. Consistent with their preference for carefully controlled RCTs, CMS preferred a far more limited regulatory experiment.

The differences between sceptics and advocates can in part be explained by reference to the politics of their respective epistemological commitments. the FDA 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. Critics of the relabeling, by contrast, argued for large-scale RCTs as the only credible basis on which to change established clinical practice.

We have already described how the FDA had embraced pharmacogenomics and personalised medicine and that this shift was accompanied by an epistemological shift in favour of genomic knowledge of the mechanics of inter-individual variation in drug response. In their seminal study of the Evidence-Based Medicine movement, Timmermans and Berg suggest that it operates with an epistemology which is "overwhelmingly empiricist and grounded in epidemiological and statistical reasoning." Research on comparative effectiveness of clinical interventions prioritises questions about what works, and what works best; "How the intervention works, physiologically ... is less relevant."[81]

The irony here is that the primacy of the RCT within the empiricist frameworks of Evidence-Based Medicine and Health Technology Assessment can in part be laid at the door of the FDA, whose championing of this research paradigm from the late 1950s onwards has been a major factor in its hegemonic status within the contemporary clinical research system.

Power

FDA's failure to achieve widespread adoption of pharmacogenetic testing for warfarin illustrated the limits of the agency's power. The lack of any *directive* power to change medical practice was clearly demonstrated by its failure to overcome clinical resistance and the scepticism of payers. Its *conceptual* power was challenged by those who rejected FDA's willingness to embrace restrospective data and who argued instead for large-scale RCTs as the only credible basis on which to change established clinical practice.

Given the limits of its power in the postmarket space, why did the FDA stake so much political capital on an intervention in this arena? Relabelling provided two chief potential advantages to FDA: a faster return on investment and a lower risk to its reputation. With regard to the first part of this calculus, the FDA's promotion of personalised medicine within the premarket space involved developing guidance on the use of pharmacogenomic data in drug development. The long timeline for pharmaceutical R&D meant that this activity would take many years before it had an impact in the clinic. By contrast, the relabeling of existing drugs was a route to far more rapid clinical adoption of pharmacogenomics; it promised to be the low-hanging fruit of personalised medicine. If successful, it would act as a boost to the whole personalised medicine project and affirm FDA's central role in that project, thus addressing the agency's institutional interest in enhancing its authority and influence.

The second advantage was that it presented less reputational risks than activity in the premarket space of the New Drug Approval (NDA) process. FDA has been under sustained

and intense political pressure with regard to the impact of the NDA process on pharmaceutical innovation since the 1970s.[82] It is therefore cautious in its approach to the application of pharmacogenomics on drug approval, as any imprudent move would present a far greater risk to its reputation. When the agency wanted to begin to look at genomic data which might impact on drug approvals it created a space outside the formal NDA process – the Voluntary Genomic Data Submission. It referred to that new pre-regulatory space as a 'safe harbour'.[83] Here we suggest that the relabeling project was an attempt to create another safe harbour, a space within which the FDA could experiment with the application of genomic data in regulatory science without fear of attracting political criticism. The postmarket space is not without its pressures, most notably around decisions to remove products from the market, but it has not attracted the degree of sustained political pressure which surrounds NDA. Operating in the safe harbour of postmarket controls the agency could then apply lessons it learnt in the postmarket space in the more politically fraught premarket space. In this sense, it was precisely the agency's limited power in the postmarket space which made it an attractive environment for regulatory experiments. Had FDA enjoyed greater power in this space, then its activities would likely have attracted greater political scrutiny.

Promissory regulation

> "Despite the scaling up of the two experiments, they did not produce final certainty or solve the problem that regulators set out to address."[84]

The relabeling project is not simply a regulatory experiment; it is also an example of promissory regulation. It seeks to shape markets; the advice contained within these label updates is performative of a particular sociotechnical future, as well as a summary of the state of the art in the science of warfarin pharmacogenetics. Thus in this case we can talk not simply of regulatory experiments, but of promissory experiments.

The shift from controlled trial to real-world experiment can be understood as a move from 'appraisal' to 'commitment'; a shift from merely seeking to understand the potential of pharmacogenomics, to a desire to put it into practice. Why the FDA had become such passionate advocates of personalised medicine is a topic for another paper. Advocacy in itself was not something new to the FDA, its championing of the randomised control trial provides a historical example of its role as a promissory organisation, albeit one firmly located in its mission as a protector of public health. What seems novel here is that senior FDA officials were vigorously championing the clinical adoption of a specific technological application and doing so without a labelling change which mandated the recommended course of action. Given how strenuously the medical profession has sought to defend its borders, keeping the firmly FDA out of clinical practice, then the warfarin relabelling might be characterised not as an experiment but as a badly planned and poorly executed foray into enemy territory. Such tactical disarray is perhaps an inevitable outcome when an organisation as large as the FDA seeks to reorient its mission, but if one accepts that the agency might have gained a better outcome had it waited for more

data, then it can also be understood as the tragic but unavoidable outcome of the practice of promissory regulation, and, more broadly, as a temporal dysfunction endemic in policy responses to promissory science.

The repeated prioritisation of the imminent can and should also be understood as evidence of an institutionalised reflex blindness to longer term temporal frames of reference which is an entrenched part of the 'timescape' of liberal democratic political culture. The analysis presented here can probably be taken to add empirical depth to wider calls for science policy to detach itself both from near-term thinking and elite stakeholder capture.[85]

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