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Neoliberal technocracy: explaining how and why the US Food and Drug Administration has championed pharmacogenomics.

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Abstract

By 2004 the FDA had emerged as a champion of pharmacogenomics as an exemplar for novel approaches to drug development. This was made clear in 2004 when the agency released a wide-ranging report which positioned pharmacogenomics at the heart of a broader regulatory reform agenda. The Critical Path initiative addressed declining productivity of drug development by suggesting that the problem was a mismatch between the rapid pace of discovery in post-genomic biomedicine and the antiquated development process for new drugs. Framing their work in this context FDA officials reconceptualised their role in the innovation process, in what was the first programmatic statement of a shift from a strictly gate-keeping role to a more collaborative or facilitative role as enablers of innovation. This paper will seek to locate the FDA's emergence as a champion of pharmacogenomics in the broader politics of pharmaceutical regulation in the USA. In making a contribution to the pharmaceuticalisation literature this paper will draw on the work of John Abraham (2010) who has argued that one of the primary drivers of pharmaceuticalisation has been "deregulatory state policies" and on Williams et al (2011) who have argued that the changing relationship between regulatory agencies and the pharmaceutical industry is an important dimension of pharmaceuticalisation. This paper links this to the promotion of pharmaceutical futures such as pharmacogenomics and explores how this shift is also closely related to the trend towards a risk management approach to pharmaceutical regulation. The role of Bush appointees in the development and promotion of the Critical Path agenda will also be examined.

Introduction

In 2009 Margaret Hamburg, Commissioner of the US Food and Drug Administration gave a speech at the American Association for the Advancement of Science. She spoke in visionary terms about the expectations which surrounded the genomic turn in the life sciences and about its potential impact on pharmaceutical regulation:

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 ...

In these, the early days of the genomic age, we are trying to adapt our thinking, our regulatory system, our models of drugs development, research, clinical trials and the very way we look at, gather and analyze data to a new reality. (Hamburg, 2009)

In setting out the potential positive impact of genomic science, Hamburg was echoing what had become a well-established position in the FDA. Pharmacogenomics is the use of genomic science to study human variability in drug response. Proponents of pharmacogenomics suggest that it will lead to a new era of personalised medicine through a fundamental transformation in the drug discovery and development process. Whilst currently clinical trials are designed to observe effects in populations, the use of pharmacogenomics will provide information on inter-individual variation in drug response. Although trial enrichment and population stratification are not novel, the promise of genomic biomarkers is that they will encourage the widespread systematic use of such techniques, both in discovery and development but also in clinical practice where the use of pharmacogenomic tests will help to identify those patients most or least likely to benefit from a drug.

In her 2009 speech Hamburg went on to link the science of genomics to the regulatory science practised by the FDA, and her argument echoed a thesis advanced many times by a variety of actors: the fruits of the Human Genome Project would include both health benefits and economic growth:

A robust, state-of-the-art regulatory science discipline is essential to FDA's work. But more than that, it represents an important driver of our nation's health, the health of our health care industry, and the health of our economy. It is a field of endeavor that must be fully embraced by academia, industry and government.

What relevance does this have for scholarship on pharmaceuticalisation? In their 2011 review Williams et al highlight a number of current trends which they see as critical to pharmaceuticalisation. One is the lowering of regulatory standards and the transformation of regulatory agencies into facilitators of innovation. Another is the creation of pharmaceutical futures, a trend which they exemplify with the example of pharmacogenomics. Williams et al do not link these two trends, but in this paper I seek to bring them together. I argue that the FDA's articulation of its new role as agent of innovation was inextricably linked to its vision of a genomic future for pharmaceutical R&D, and that the framing of this policy was, to a significant extent, shaped by a neoliberal policy agenda of permissive regulation, an orientation not new to the Agency, but amplified by the appointment of pro-industry officials to senior positions in FDA by the Bush administration in 2001, just at the time when FDA staff were beginning to articulate the agency's policy towards pharmacogenomics. Subsequently, when the Vioxx scandal brought political pressure for a reversal of the policy of permissive regulation and a return to a more

stringent approach to protection of public health, senior FDA officials presented pharmacogenomics as a technocratic solution to the political tensions inherent in the exercise of their regulatory authority. Finally, I suggest that the FDA's advocacy of a pharmacogenomic future must be understood as an expression of the broader ambitions of the US government to maintain its competitive advantage in the global bioeconomy.

Methods

My initial research in this area was conducted in a series of projects between 2004 and 2008 including commissions from Health Canada for an overview of global developments in the regulation of pharmacogenomics. Desk research took the form of a literature review encompassing regulatory guidance documents, scientific papers, and grey literature including policy reports, commercial industry surveys and industry news publications. Field research took the form of expert interviews with industry executives, regulatory officials and clinicians and participation in scientific meetings and industry conferences. Since then participation in industry and scientific conferences, and a variety of 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. More recently I have supplemented this field work with additional interviews with industry and regulators and have 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, as well as other grey literature and scientific papers.

Conceptual framework and historical background

A substantial body of scholarship informs our understanding of the history and contemporary operation of the FDA's regulatory regime for pharmaceuticals, but in this paper I engage primarily with recent work from four scholars: Daniel Carpenter's highly detailed history of FDA's regulation of pharmaceuticals, which spans around seventy years from 1938 - 2008 (Carpenter, 2011); John Abraham and Courtney Davis more contemporary analysis which focuses on the last thirty years (Davis and Abraham, 2013) and Edward Nik-Kah's historical exegesis of the role of the Chicago school of economics in the late sixties to early 1980s .

Corporate bias posits an intimate relationship between public policy and commercial interests, in which representatives of the pharmaceutical industry are granted "privileged access to the state, over and above any other interest groups ... setting the agenda for regulation" (p33) In recent decades, *neo-liberal* corporate bias has been characterised by the pursuit of deregulatory reforms justified by the assumption that the interests of patients are aligned with those of industry in seeking acceleration of the approval process as part of a broader relaxation of

regulatory standards. Although their work posits that industry demands have become increasingly influential in shaping the regulatory regime over the last two to three decades, they distinguish their neoliberal corporate bias theory from the established regulatory capture model. Corporate bias theory does not privilege the relationship between regulatory agency and regulated firms; industry's strategic access to the policy-making process encompasses executive and legislature, as well as the regulatory administration.

If the narrative arc of Abraham and Davis's work is the decline in FDA's power, Carpenter, by contrast, seems more interested in understanding how the agency has retained so much of its power. He offers a more pluralist model of the regulatory regime, in which a greater diversity of actors is accorded influence, because his model centres on reputation management as the critical driver of organisational behaviour of regulatory agencies, and the management of reputation requires attention to multiple audiences including:

... the political and judicial authorities who endow organizations with power; interest groups and civic associations; organizations of professional and scientific expertise; media syndicates in print and broadcast, the mass publics who digest the information produced by these syndicates; the companies, corporations, and citizens who are governed by agencies; the clienteles who rely upon agencies for benefits and for order. (Carpenter, p34)

Carpenter also emphasises how the FDA's reputation as a *scientific* organisation was rooted in dense networks of association: "between the agency, its committee system, universities and clinical researchers, pharmaceutical firms, and specialized medical and scientific societies and their members." (Carpenter, p303)

From the Kefauver Amendments to the era of permissive regulation

Although there are important conceptual differences between the work of Carpenter and that of Abraham and Davis, they agree that since the enactment of the 1962 Kefauver Amendments to the FDCA which defined contemporary pharmaceutical regulation, the FDA has been under increasing pressure to adopt a more permissive and less stringent approach to regulation, a critical point of departure for this paper.

Developed as a response to what was perceived as a profound crisis in drug safety following the international scandal surrounding the drug Thalidomide, the 1962 Kefauver Amendments was the legislative framework through which the three critical components of the contemporary pharmaceutical regulation regime were defined: premarket review of safety and efficacy, the three-phase system of clinical trials, and the requirement for randomised control trials (RCTs). Only the first of these requirements was explicitly set out in the new legislation, but such was the political support for regulatory reform at this time, that the FDA felt empowered to radically

transform the industry's R&D process, imposing requirements which compelled firms to hire large numbers of clinical pharmacologists and to establish entire regulatory divisions from scratch in order to comply with the agency's new standards. This transformation of the pharmaceutical innovation process was carried out in the face of opposition from industry, who "steadfastly resisted any provision that strengthened the Administration's gatekeeping authority." (Carpenter, p 269)

Industry criticism continued through the 1960s and 1970s, much of it focused on the complaint that FDA was now slower to approve new drugs than its counterparts in other countries – the so-called 'drug lag' thesis. Carpenter argues that in the 1970s review times became a concern for senior FDA managers, who began to pay particular attention to "drug lag items", creating pressure to approve drugs which had already been licensed in other jurisdictions. By the late 1970s Congress, the pharmaceutical industry and its financial investors were routinely invoking another metric – the number of NMEs approved per annum. This gave rise to the December effect – a spike in the number of drugs approved at the end of the year as FDA sought to maximise its approvals for that twelve months. (Carpenter, pp.530-1; Davis and Abraham pp.42-9).

The temporal effects of permissive regulation were formalised when the Prescription Drug User Fee Act (PDUFA) was passed in 1992, and then when PDUFA was re-authorised in 1997 and 2002. This legislation rendered FDA dependent on industry funding, with user fees now a core part of the Agency's budget, and laid out an explicit timetable for the acceleration of regulatory approval: the 1992 legislation required that by 1997 the FDA would review 90 percent of priority NDAs within six months, and then at re-authorisation the Agency was given the further target of reviewing 90 percent of standard NDAs within 10 months by 2002. (Carpenter, p.735) The transition to a more permissive era in pharmaceutical regulation was now codified in temporal performance metrics defined in statute. Furthermore, PDUFA marked a decisive shift in relations between the FDA and the regulated industry, not least because negotiations on the Act and its periodic reauthorisations have "put industry representatives explicitly at the table with top-level FDA officials." (Carpenter, p734)

In seeking to explain these changes, Davis and Abraham point to 1981 as a critical turning point. The new Reagan Administration, backed by a Republican-controlled Senate embarked on a "radical deregulatory agenda". Within weeks of Reagan's election, the FDA was being warned that a more industry-friendly attitude was now required. That year a Commission on the Federal Drug Approval Process was established, and its 1982 report made a series of recommendations designed to accelerate FDA's review of new drugs, which were subsequently enacted in the mid-1980s. These reforms coincided with a series of cuts to the FDA budget that

would see the Agency's staff decline from 8,200 in 1979 to a little over 7,000 by 1987. Critically for Davis and Abraham's model of neoliberal corporate bias, the timing of these changes predates the pressure for FDA reform which came from AIDS activists in the late 1980s, a driver of change which features much more prominently in Carpenter's narrative (as well as in the work of Daemmreich (2004)).

Support for the view that the era of permissive FDA regulation has a neoliberal pedigree is provided by Edward Nik-Kah (2014). His archival analysis documents how, a decade after the 1962 Kefauver Amendments, senior figures from the Chicago School of Economics played a leading role in orchestrating a "multidirectional attack" on the FDA's regulatory authority (p4). In December 1972 the University of Chicago hosted the Conference on the Regulation of the Introduction of New Pharmaceuticals, an event funded by pharmaceutical firms and attended by a carefully selected group of legal scholars, industry executives, pharmacologists and economists. The immediate result of the event was a volume of papers, *Regulating New Drugs*, which provided the first sustained critique of the regulatory regime established under the 1962 Amendments. Subsequently this network of FDA critics established dedicated think-tanks in the mid-'70s: the Center for the Study of Drug Development (which would in time be affiliated to Rochester University) and the Center for Health Policy Research at the American Enterprise Institute. This new industry echo chamber amplified longstanding industry complaints, most notably the drug lag thesis, but articulated them within a broader neoliberal critique of state-sponsored regulatory science "based on a presumed inherent inability of the state – or any other person – to comprehend as much as the market". (Nik-Kah, p.15)

Taken together, the work of Nik-Kah and Abraham and Davis provides conclusive evidence that the political pressures which defined a new era of permissive pharmaceutical regulation in the USA were distinctively neoliberal in their origins, character and effects. The contemporary FDA is an agency which has been starved of funds, weakening its capacity to exert its statutory authority. It is an agency increasingly reliant on industry funding, an arrangement which has required it to commit to faster review times, and more flexible and open modes of engagement with drug sponsors, thus exemplifying the neoliberal agenda of reorienting the state away from welfare provision and towards supporting industry. Finally, the FDA increasingly defines itself as an enabler of innovation, as well as a guardian of public health, and in seeking to align those two responsibilities, it promotes a neoliberal blurring of the commercial interests of firms in accelerated drug approval and the broader public interest in access to safe and effective medicines.

Regulating novel biotechnologies

Notably for the purposes of this paper, neither Carpenter, nor Abraham and Davis, have treated technology as a factor which has influenced the development of permissive regulation. However, there is a growing body of work which is primarily concerned with how regulators respond to novel biotechnologies such as gene therapy and tissue engineering, either by establishing new governance frameworks or by finding a place for new technologies within existing governance frameworks (Cambrosio, Faulkner, Salter). Hauray and Urfalino have approached the same dynamic from a different perspective: seeking to understand the politics of regulatory harmonisation and centralisation within the European Union, they describe how biotechnology has acted as an “exogenous shock” on this process.

Linda Hogle has also sought to contextualise the regulation of novel biotechnologies within the broader techno-politics of biomedical governance. As Hogle notes in her study of the creation of regulatory framework for tissue engineering, this regulatory framework was developed in a political climate in which there was little inclination to constrain nascent, struggling industries. ... changes were made in federal regulatory institutions that reflected broader political initiatives intended to facilitate the flow of capital while decreasing the state's role and responsibility for product safety and oversight. (2009, p.718)

Promotion of the life sciences and biotechnology is intimately interlinked with the vision of a knowledge-based economy which emerged in the US and Europe in the 1980s (Cooper, 2008; Jassanoff, 2005) The rise of biotechnology has been driven by multiple forms of state activism: regulatory reform, R&D investment, new mechanisms for technology transfer; and the extension of intellectual property rights. (Orsenigo, 1989). In this paper we argue that what emerged in the USA through these diverse policy initiatives was a form of network governance which we might characterise as the “translational state”: various arms of the Department of Health and Human Services (HHS), from the National Institutes of Health to the FDA, became committed to accelerating the commercial translation of biomedical research into tools for clinical practice. The FDA's championing of pharmacogenomics must be understood in the context not only of developments internal to the agency, such as the rise of permissive regulation, but in this broader context of state activism in support of biotechnology.

The FDA and pharmacogenomics

Early days: 2002-3

FDA's public engagement with pharmacogenomics began with a workshop held in May 2002. This meeting was co-sponsored by a number of industry bodies: the Pharmaceutical Research and Manufacturers Of America (PhRMA) which is the industry's main trade body in the USA, DruSafe (PhRMA's Preclinical Safety Committee), and the Pharmacogenetics Working Group

(PWG), a much smaller industry body. The meeting notice seems to have presumed a broad audience, stating that the workshop was intended for “scientists and clinicians with an interest in the role of pharmacogenomics and pharmacogenetics in drug development, and for regulatory scientists in these disciplines who are responsible for regulatory decision-making” (FDA, 2002) However, the notice also states that individuals from the FDA and the three industry bodies co-sponsoring the event will be given priority for registration.. A privileging of FDA and industry is certainly reflected in the speaker list: the workshop included a keynote address from Jeffrey M Drazen, a Harvard professor and then editor-in-chief of the New England Journal of Medicine, but, with the exception of a representative of the European Medicines Agency, all the other speakers were either from the FDA or industry. Academic scientists working in the field, and others with an interest, such as healthcare policymakers, were neither speakers, nor envisaged as the event's primary audience.

Establishing a precedent which was followed in subsequent workshops, the 2002 meeting was co-chaired by officials from FDA and industry (in this instance Larry Lesko and Ron Salerno) and FDA officials co-authored a report of the first workshop with industry participants (Lesko et al, 2003). It was described as “the first agency-industry workshop on pharmacogenetics and pharmacogenomics”. The workshop was followed by subsequent events in 2003, 2004, 2006, 2007 and 2010. The range of industry bodies co-sponsoring the events widened to encompass the Drug Information Association and the Biotechnology Industry Organisation. By the 2010 meeting it was being billed as an opportunity for networking with “colleagues from academia, regulatory authorities, industry, payors and providers” and there were more speakers from academia, but the 13-strong steering committee was populated solely by FDA and industry officials and only seven of the thirty-nine scientific advisory group were not regulator or regulatee.

These co-sponsored workshops were the not only meetings at which FDA officials talked about pharmacogenomics, and below I discuss how the agency increasingly consulted with a broader array of actors, but according to the FDA these workshops with industry were critical in shaping the Agency's approach to pharmacogenomics:

These workshops served to catalyze guidance and policy development, to build an infrastructure for regulatory review and to provide pharmacogenomics principles in drug development. (FDA, 2013, p.16)

From the outset Larry Lesko was effusive about the cooperation which the workshops engendered, suggesting that it had a far broader significance, signalling “a new openness and a new era” (Lesko, quoted in Branca 2002). To the extent that these workshops did indeed play a critical role in defining the emergent regulatory framework for pharmacogenomics, then it

would appear that this was a policy process characterised by what Abraham and David have termed neoliberal corporate bias, both in terms of the process but also its policy outcomes. In 2004 Lesko and Woodcock made it clear that they wished to ensure that the FDA's actions were acceptable to industry and did not threaten corporate interests.

The FDA has become a proactive and thoughtful advocate of PGx and PGt, and believes that as a public health Agency it has a responsibility to play a leading role in bringing about the translation of PGx and PGt from bench to bedside. The FDA also realizes that it can hinder innovation and become a regulatory barrier in the translational process if it is not careful with its guidance, policies and procedures.

Furthermore they argued that transnational harmonisation was important because of the need to ensure that the new regulatory paradigm develops "in a way that facilitates and not complicates the drug development process." (Lesko and Woodcock, 769)

How far the FDA might be willing to push industry in a direction which it did not want to go became clear in the published report from the first workshop in its discussion of whether industry might be compelled to provide FDA with the genomic data it was gathering in clinical trials. This issue came up in relation to the topic of toxicogenomics, on which the authors reported that the workshop participants felt that it would be "premature for the FDA to write a guidance for industry", in large because of the rapidly evolving nature of the science, but the report also noted several problematic issues which would arise were a guidance to be developed, the last of these was "whether a guidance would compel a company to engage in genomics research even if it was not prepared to do so." (Lesko et al 2003, p348).

The question of compulsion was central to the Voluntary Genomics Data Submission process, the FDA's first major policy initiative in this area and an initiative which arose directly from the workshop discussions. The workshop had confirmed what was already known: many firms were gathering genomic data in their clinical trials, but industry was unwilling to share that data with the FDA, fearing such disclosure might have negative consequences. In the words of the report: "... sponsors have concerns that genomic-based data would be acted on prematurely by regulatory authorities to interfere with or add to the cost of drug development." (Lesko et al, 2003 p356). One solution would have been for the FDA to demand that industry share the data as part of its regulatory submission, but that was not the preferred policy. Instead the FDA instituted a new *voluntary* process which would permit firms to share pharmacogenomic data with the agency in a forum outwith the formal regulatory decision-making system. The FDA thus signalled that it was as keen as industry to ensure that its new commitment to pharmacogenomics should not complicate or increase the cost of drug development.

From the outset, then, the FDA's genomic turn bore the imprint of the longstanding pressure on the agency to minimise the regulatory burden on pharmaceutical firms and to adopt a more flexible and cooperative approach to interactions with industry. However, the impact of this well-established trend was amplified by a change of administration, as Bush-appointees took charge at the FDA following the 2000 Presidential election.

The Bush agenda in the FDA

It was an accident of history that CDER's engagement with pharmacogenomics coincided with the end of the Clinton administration and the entry of George Bush into the White House. What cannot be considered accidental is the role played by Bush appointees to the FDA in shaping the Agency's approach to pharmacogenomics, which was seen as a technological means to broader political ends. The Bush administration made a series of appointments to the FDA, bringing individuals into senior posts who were widely seen as industry-friendly. These included Dan Troy as Chief Counsel, Mark McClellan as Commissioner, Randall Lutter as deputy commissioner for Policy and then in 2005 Scott Gottlieb as Deputy Commissioner for Scientific and Medical Affairs. The FDA's neoliberal critics had stormed the citadel: Troy, Lutter and Gottlieb had all worked for or with the American Enterprise Institute (Carpenter, 2010), one of the agency's most vocal neoliberal critics. Troy's appointment was noteworthy as the first time a political appointment had been made for the post of the Agency's senior legal adviser. At the time of his appointment Troy was working for the DC law firm Wiley, Rein & Fielding where his clients included many major pharmaceutical firms. The industry-friendly nature of the Bush-era FDA leadership was exemplified by Troy's pursuit of the policy of pre-emption: the principle that a firm cannot be sued for negligence in the development or marketing of a product if the FDA has approved the product. The Bush administration pursued the policy of pre-emption as a way to protect a variety of industries from consumer protection legislation and the danger of litigation, but some have suggested that the policy was pursued most vigorously at FDA. Troy used his position at the FDA to intervene on the side of industry in a succession of law suits, famously on one occasion even inviting industry representatives to come to him with cases, and the pre-emption doctrine was enshrined in regulatory policy in a preamble to the updated regulation on drug labelling (Mencimer, 2008).

In this period the FDA produced a number of policy documents which sought to extend the neoliberal policy of permissive regulation by emphasising the importance of accelerated approval and cutting the cost of pharmaceutical R&D. Initiatives included a joint programme with the National Cancer Institute to "streamline cancer drug development" and a new commitment to reduce the time taken to review medical devices (FDA, 2003 a/b). These and other initiatives were brought together in the Agency's 2003 strategic report which set out a

new risk management approach to regulation which was targeted at reducing regulatory barriers. The report declared that “Steps to reduce the time, cost, and uncertainty of developing new drugs and devices are ... important public health priorities.” (p11) This was not the only goal set out in the report but it was given primacy as the first of the agency's four overarching objectives. To meet this primary objective, drug approval was to be subject to continual scrutiny in order to reduce avoidable delays. The final goal detailed as part of this key overarching objective related to emerging biotechnologies:

Direct agency research programs and develop standards to effectively handle emerging technologies, especially in areas of pharmacogenomics, gene therapy, and combination devices. The objective is more efficient and rapid translation of new scientific developments and breakthroughs into safe and effective medical products. (FDA, 2003, p14)

Thus the FDA's approach to pharmacogenomics, and other novel biotechnologies, became more firmly framed as part of the agenda to accelerate drug approval and reduce the cost of drug development, which had been declared a priority by the Bush-appointed Commissioner Dr Mark McClellan. *The New York Times* reported in 2003 that McClellan believed that clinical research could be accelerated through the use of genomics:

One factor in the cost of new drugs is the necessary tests for safety and effectiveness. There, Dr. McClellan said, the agency can make a difference. He is looking for better ways of deciding early whether a drug is going to work, using genetic markers, for example, that might indicate whether a drug is converting a cancer cell into a normal one. (Kolata, 2003)

In the FDA's 2003 strategic report the regulatory application of science was only one part of the agency's neoliberal reform agenda, but the following year saw a distinct technocratic shift in the policy discourse.

The Critical Path – new tools for a new century

In 2004 the FDA launched the Critical Path Initiative (CPI), an ambitious programme of work whose goal was a fundamental re-engineering of the pharmaceutical R&D process based on the development of new scientific tools for product development. Pharmacogenomics was one component of this broader regulatory reform agenda. The report was entitled “Innovation or stagnation” and this Manichean view of the prospects for industry R&D framed a gloomy analysis:

the vast majority of investigational products that enter clinical trials fail. Often, product development programs must be abandoned after extensive investment of time and

resources. This high failure rate drives up costs, and developers are forced to use the profits from a decreasing number of successful products to subsidize a growing number of expensive failures. Finally, the path to market even for successful candidates is long, costly, and inefficient, due in large part to the current reliance on cumbersome assessment methods. (FDA, 2004, pii)

As the last clause suggests, the report framed the productivity decline as the consequence of a mismatch between the rapid pace of discovery in post-genomic biomedicine and the antiquated development process for new drugs. Thus problems which had been laid at the feet of the agency - its bureaucratic caution and administrative inefficiency - were now reframed as essentially technical issues which could be addressed through the better appliance of science.

Not enough applied scientific work has been done to create new tools to get fundamentally better answers about how the safety and effectiveness of new products can be demonstrated, in faster time frames, with more certainty, and at lower costs. In many cases, developers have no choice but to use the tools and concepts of the last century to assess this century's candidates. (FDA, 2004, p.ii)

The mapping of the human genome plays an important role in framing the report's argument. For instance, the opening chapter begins:

The sequencing of the human genome four years ago raised widespread hope for a new era in the prevention and treatment of disease created by the ongoing investment in biomedical research. But that new era has not yet arrived. Instead, 2000 marked the start of a slowdown in new drug and biologic submissions to regulatory agencies worldwide. (FDA, 2004, p.3)

Faced with these challenges the FDA proposed the creation of a new "product development toolkit - containing powerful new scientific and technical methods" (p.ii). These would include "biomarkers for safety and effectiveness, and new clinical evaluation techniques" (p.ii). There was the promise of a review of fundamental aspects of the drug approval process such as clinical trial design. The report argued that the FDA was in a uniquely powerful position to reframe biomedical innovation because its role as a regulator gave it the authority to create the standards which shape the biomedical innovation process:

"... we have an important role to play. Because FDA's standards are often used to guide development programs ... FDA is uniquely positioned to help identify the challenges to development..." (p.iii)

This championing of socio-technical futures exemplified the gradual shift in the organisational identities of FDA: its traditional role as guardian of public health had not been relinquished, but it was now supplemented by a new role as enabler of innovation (Williams et al 2011). In this regard the CPI was a logical extension of the neoliberal policy of accelerated approval. This continuity with established trends should not diminish the significance of what was in effect the first programmatic statement of a new technocratic turn in that policy. Emboldened by a Bush administration intent on bending government science to the needs of industry, and inspired in part by the rapid pace of progress in genomics, Lester Crawford, then Acting Commissioner for the FDA, described the CPI as “an undertaking through which the FDA, in effect, has accepted a share of responsibility for the development of novel drugs.” (Crawford, 2004).

Pharmacogenomics policy had begun with the creation of new forms of industry/FDA collaboration and a new space for sharing data outside the regulatory system, now what was proposed was a further blurring of the boundary between industry and regulator. However, in contrast to the co-sponsored workshop series initiated in 2002, the CPI was envisaged as a far broader coalition of actors. The collaborative networks which emerged from the CPI, such as the Microarray Quality Control Consortium, were public-private partnerships in which academic scientists played an important role.

Furthermore the CPI was linked to a broader policy agenda within the Department of Health and Human Services under the two Bush-appointed secretaries: Tommy Thompson and Mike Leavitt. Thompson initiated an inter-agency Medical Innovation Task Force which linked FDA to the National Institutes of Health (NIH) and the Center Medicare Medicaid Services (CMS). NIH had embarked on its own initiative – the NIH Roadmap – a strategy which emphasised translational research, under the leadership of the new NIH Director Elias Zerhouni, a clinician and scientist who was also a serial entrepreneur, as the founder of a number of medical imaging companies prior to his appointment. Subsequently, Bush's second secretary of HHS Mike Leavitt, would initiate a second inter-agency programme, this time focused specifically on personalised medicine/pharmacogenomics.

However, despite its apparent fit with the broader ambitions of the US government to maintain its competitive advantage in the global bioeconomy, the grand ambition of the FDA's Critical Path initiative was stymied in 2004 by the unwillingness of Congress to provide additional funds for FDA's regulatory science activities. In 2007 an FDA-commissioned report on the state of regulatory science reported that “Despite its predicted impact on safety and reduction in the time and cost of development of new lifesaving products, the initiative, for lack of funds, has only begun to be implemented.” (FDA, 2007, p.18) Praising what it described as “a serious commitment in sustaining momentum for the Critical Path Initiative, primarily due to heroic

efforts by several senior FDA administrators," the report's authors stated that even genomics, which was the area of emerging science which had most advanced in FDA, was "in only the rudimentary stages of development." (p25)

The Congressional funding failure suggests a lack of political consensus on the FDA's new mission to facilitate innovation by advancing regulatory science. It is possible that political support for the FDA's neoliberal technocratic agenda may have been more forthcoming had the Vioxx crisis not erupted later that year.

Vioxx and pharmacogenomics – from no-win to win-win

Concerns about FDA's regulatory performance were front-page news as a result of safety concerns about the antiarthritis drug rofecoxib (Vioxx), the first of a new class of drugs called COX-2 inhibitors. Merck, Vioxx's manufacturer, withdrew the drug from the market after new clinical data emerged demonstrating that patients taking the drug were at three times greater risk of a heart attack than those on alternative treatments or placebo. Officials at the FDA's Office of Drug Safety complained to Congress that the "FDA and its Center for Drug Evaluation and Research are broken." Senator Hillary Clinton typified the political criticism when she referred to the agency's "battered reputation", following the resignation of Lester Crawford in 2005 (both cited in Carpenter, p.738). Public opinion polls showed a decline in confidence in the FDA from 80% in the 1970s to just 36% in 2006 (FDA, 2007).

Given that the FDA was widely viewed as failing in its core mission, this was perhaps not the ideal environment in which to pursue an expansion of the agency's mandate through the CPI. As one industry report put it: "Critical Path seemed to drop off the radar as public concern veered in the direction of drug safety, and politicians railed about the "too-cozy" relationship between FDA and the industry" (Clinton and Wechsler, 2006). However, the report noted some progress in establishing the legal basis for cooperation between FDA, industry and academia and the imminent announcement of CPI research priorities backed with some funding. Furthermore, Janet Woodcock was reported presenting pharmacogenomics as a solution to the problems which Vioxx had exemplified:

'We're beat up for not approving things that ultimately prove to be beneficial because we're uncertain about the benefits ... We're beat up if we approve something and then a subgroup turns out to be harmed by it. It's a no-win situation for the regulators, because there are always going to be people who benefit and people who are harmed.' (Woodcock cited in Clinton and Weschler, 2006)

What critics of the FDA had seen as a political failure of regulatory judgement, Woodcock presented as the outcome of inadequate science.:

the industry and the agency need to move from a population-based model, in which drugs are tested on broad pools of patients, to a more targeted approach in which clinical development focuses on patients most likely to benefit from a drug. (Clinton and Weschler, 2006)

In this technocratic vision there are no bad drugs, just inappropriate patient populations. The traditional public interest model of pharmaceutical regulation operates with a calculus based on a generalised public and a generalised public interest, one which, whilst acknowledging that adverse events may only occur in a minority, deems that if those events are severe enough and frequent enough then the greater good is best served by a blanket ban. In the wake of one of the FDA's most serious crises, when the agency's willingness to enforce its established standards was doubted by many commentators, Woodcock suggested that pharmacogenomics could solve the political dilemma of risk-benefit evaluation by reducing it to the technical challenge of identifying those most likely to benefit and those at greatest risk of harm. The FDA's turn to pharmacogenomics is not the origin of this risk management approach to pharmaceutical regulation, but it provides a new scientific rationale for that policy, and frames the transition not as an ignoble retreat from established scientific standards, but a triumphant progress towards new ones.

The Bush era is now long passed, but the FDA has continued to frame pharmacogenomics as a means to accelerate drug approval. In her 2011 presentation to Congress on negotiations for re-authorisation of the user-fees regime, Janet Woodcock outlined a series of "program enhancements" which were being developed in consultation with industry and other stakeholders. The second of these enhancements comprised a number of initiatives under the heading "Enhancing Regulatory Science and Expediting Drug Development" and the third of these was "Biomarkers and Pharmacogenomics". This section opens with the statement:

Pharmacogenomics and the application of qualified biomarkers have the potential to decrease drug development time by helping to demonstrate benefits, establish unmet medical needs, and identify patients who are predisposed to adverse events. (Woodcock, 2011, p15)

The structure of the sentence is illuminating: pharmacogenomics and biomarkers offer a number of important benefits, such as addressing unmet clinical needs and identifying those at risk of adverse drug reactions, but the primary benefit, which precedes and thus frames these, is the potential for accelerating drug development. It is a questionable construction since pharmacogenomics might bring all the secondary benefits without decreasing development time, but it is this framing which has defined the FDA's engagement with genomic science.

Discussion

“Through their risk-based frameworks regulators are attempting to redefine political and public expectations of what they should achieve, what they should be held responsible for, and what they should not.” (Black , 2005, p174)

The emergence of the modern pharmaceutical regulatory regime in the wake of the 1962 Kefauver amendments was, as Carpenter suggests, also a redefinition of the role of the FDA, with the Agency's role as “protector” fusing with its image as a “gatekeeper”. The rise of efficacy regulation was “an organizational achievement” which placed the new process for FDA drug review at the nexus of market, state and society. If biotechnology has reconfigured that nexus, then the Critical Path Initiative and its constituent programmes, exemplified by pharmacogenomics, can be seen as the FDA's attempt to ensure it remains at its heart, and in doing so FDA has again expanded the scope of its identity, enhancing its new role of as an enabler of innovation.

Carpenter's model of reputation management as a driver of bureaucratic behaviour is consistent with the view that FDA was compelled to embrace the genomic turn in the life sciences as a necessary means to ensure its continuing relevance. This may have begun as a process of catching-up, as regulators' sought to understand industry's investment in genomics, but the ambitions of the CPI are far bolder. It seeks to place the FDA at the heart of the genomic turn in the life sciences, by giving them a pivotal role as the orchestrators of new forms of transnational public-private partnership, leveraging their established role as standard-setters for scientific experiment and technological development in contemporary life sciences. The networks of academic and industry collaborators formed through CPI programmes exemplify Carpenter's model of pluralist regulatory politics.

The FDA's eager embrace of pharmacogenomics in the Critical Path report perhaps offers something of a corrective to much work on the regulation of novel biotechnologies which has tended to focus on the profound challenges that policymakers face in responding to new biotechnologies. The FDA's approach to pharmacogenomics and the broader Critical Path agenda would seem to turn that logic on its head. Pharmacogenomics is not a governance problem to be solved: it is a solution to problems within the established regulatory regime. Thus whilst some novel biotechnologies, notably GM crops, seem to have presented severe challenges to the legitimacy of a technocratic mode of governance (Radaelli, 1999), pharmacogenomics was seized upon by senior FDA officials as a technocratic solution to the political tensions inherent in the exercise of regulatory authority, tensions which were exacerbated by the public unease engendered by the neoliberal policy of permissive regulation.

I do not wish to suggest that pharmacogenomics was promoted by the FDA *only* because it aligned with permissive regulation, or even that this was the sole *framing* of the issue: FDA officials like Janet Woodcock have consistently advanced the argument that pharmacogenomics can deliver important public goods – new drugs with enhanced safety and effectiveness achieved by a narrower targeting at a biomarker-defined sub-population. Consistency with the neoliberal turn to permissive regulation is neither the sole driver of FDA's policy, nor can we suggest it is in itself a *sufficient* cause for promotion of pharmacogenomics, but it would, on the evidence presented here, appear to be a *necessary* cause: firstly, because it seems to have been impossible for FDA to discuss pharmacogenomics without linking it to the goal of faster and cheaper drug development; and secondly, because Abraham and Davis's theory of neoliberal corporate bias is consistent, not just with the framing of pharmacogenomics, but also the policy process (the co-convened regulator/industry workshops so central to FDA policy development) and the policy outcomes, (or, in Abraham's words' "the lack thereof") .

In this latter respect, it is noteworthy that the FDA has failed to mandate biomarker stratification, despite the agency's oft-stated belief that it is the most promising device in the new toolkit of post-genomic regulatory science. FDA officials acknowledge that progress in personalised medicine has been slower than many hoped, but they continue with a voluntaristic approach to genomics which allows industry to treat biomarker stratification as a rescue strategy of last resort. In the vast literature which addresses the obstacles to progress in personalised medicine, one option which is almost never discussed is that FDA should make genomic data submission mandatory. This is in stark contrast to the last time the FDA declared the pharmaceutical innovation process broken. Following the 1962 Kefauver amendments the FDA used its enhanced powers to impose a new regulatory regime which radically transformed the industry's R&D process, imposing significant additional costs. If the FDA's approach to pharmacogenomics offers new insights into the current state of pharmaceutical regulation then we have as much to learn from the silences in this policy area, the choices which have not been discussed, as we can glean from the policies which have been pursued.

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Response to reviewers' comments

Author's responses in italics

I am grateful to the reviewers for their highly constructive comments which have been most helpful in revising the paper. I outline below how I have responded to their feedback, including some justification for the small number of points where I respectfully disagree with the comments made.

Reviewer #1

1.1 The author isolates two theses on the first page of text: First, pharmacogenomics was championed by the FDA because it allowed a permissive risk-management approach to regulation, and second, it was championed to maintain competitive advantage in the global bioeconomy. I find the second thesis plausible, and supported by evidence in the paper (though I think that this is a really interesting story and I would have been interested to see more detail). The first thesis, though, is not well-supported by evidence, and in fact may even be somewhat undermined by the evidence presented.

I respond to the specific points where they are repeated by the reviewer below

1.2 I suspect that part of the problem here is the attempt to shoehorn this material to fit with John Abraham's central theses, when actually what is going on here seems more complicated. I'll make a case for this in my more specific comments below.

Again, I respond to specific points below, but on the general point, as above I have now paid more attention to discussion of how the FDA's approach to PGx must also be understood in terms of Carpenter's model of reputation management and network governance.

1.3 Page 4: On drug lags, the author should see:

Daemmrich, Arthur. "Invisible Monuments and the Costs of Pharmaceutical Regulation: Twenty-Five Years of Drug Lag Debate." *Pharmacy in history* (2003): 3-17.

and

Nik-Khah, Edward. "Neoliberal pharmaceutical science and the Chicago School of Economics." *Social Studies of Science* (2014): 0306312714520864.

Both of these present much more nuanced versions of the history of concern over drug lags.

Nik-Kah's paper is now discussed in some detail, I was unable to cite the working draft at time of submission because very reasonable restriction set by the author, and I am very grateful that the paper is now published and its very important arguments can be worked into my paper.

1.4 Page 6:

I kept returning to the definition Abraham gives of neoliberal corporate bias (NCB), and I think that it is very difficult to separate any particular instance of NCB from traditional "capture". It certainly looks as though regulators like the FDA are perpetually being captured by the pharmaceutical industry - and perhaps this is why some of the most effective regulation of the industry in the U.S. today is happening from the Government Accountability Office (through Corporate Integrity Agreements) and Congress (through its new Sunshine Act and the like, administered roughly speaking through Medicare). This is not to say that there isn't NCB. But I think that Nik-Khah (above) has a better strategy for identifying and arguing for NCB. Perhaps we should see these things as non-competitive, and NCB as providing background support for capture.

I have delineated what, for purposes of this article, are key differences between capture theory and NCB, firstly the NCB i.e. its neoliberal orientation (for which I draw on both Nik Kah and Abraham and Davis) and secondly the fact that it implicates not only the regulatory agency (the bureaucracy) but also the executive and legislature.

1.5 Page 7:

Like the author, I think that it's fascinating that the FDA got involved in pharmacogenomics. However, we might see this as running counter to the interests of the pharmaceutical industry, if we accept Hedgecoe and Martin's argument that the industry's interest in pharmacogenomics is superficial, because it stands too much to lose from identifying sub-populations for its products:

Hedgecoe, Adam, and Paul Martin. "The Drugs Don't Work Expectations and the Shaping of Pharmacogenetics." *Social Studies of Science* 33.3 (2003): 327-364.

The paper did not clearly enough articulate one of its central arguments: although FDA has championed pharmacogenomics as a critical component of the future of pharmaceutical innovation, it has not sought to impose that on industry, hence for instance, voluntary genomic data submissions. As I stated in the conclusion, this voluntaristic approach is in contrast to the mandating of a new regulatory framework and thus a new innovation process in implementation of the 1962 Kefauver Amendments. The lack of mandatory measures is in substantial part precisely because the neoliberal pressures on FDA has rendered it incapable of mandating a regime which might run counter to interests of pharma industry as presently constructed. Hence the attention to industry concerns from the outset of this policy process and the stated concern by Woodcock and Lesko to ensure PGx policy does not "hinder innovation and become a regulatory barrier".

1.6 Page 9:

"Thus the FDA's approach to pharmacogenomics became more firmly embedded within the agenda of accelerating drug approval and reducing the cost of drug development ..."

I think that the author is only entitled to say that these are "rhetorically linked to", rather than "embedded within". In fact, what the author presents here (especially on the next page, but also Woodcock quoted on subsequent pages) looks to me like Bush administration sci-fi enthusiasts trying to drag the industry along into the 21st century. They bought into a certain level of hype about the Human Genome Project, and technoscientific solutions to the problems that they were identifying.

I have rephrased this sentence to more clearly state my meaning – it now reads: " Thus the FDA's approach to pharmacogenomics, and other novel biotechnologies, became more firmly framed as part of the agenda to accelerate drug approval and reduce the cost of drug development" The language of framing is used more consistently throughout the paper.

Reviewer 2

This is a well-structured and nicely written paper which is strongly linked to the debate about pharmaceuticalisation and has the potential to make a valuable contribution to the theoretical discussion in this area. The core argument about the changing nature of the US drug regulatory regime and the FDA's role in promoting pharmacogenetics (PGx) are of significance. In particular, the focus on the Critical Path Initiative as a key moment provides real insight into these broader developments. The paper is original in doing this and the evidence presented is largely convincing. However, there are a number of areas where it could be improved, as well a series of more minor corrections.

2.1 The introduction needed to elaborate further on the nature of the problem/ question and the conceptual debates being addressed in the paper (see also comments about the conclusion). There is a clear argument running through the paper, but this is not always made explicit. For example, the author(s) nicely trace the way in which FDA policy is shaped by industry and how this took a particular technological form with the launch of the Critical Path Initiative. However, this is not really flagged at the start or linked to the conceptual debate.

The introduction now describes the paper's core arguments, see additional material in paragraph beginning "What relevance does this have for scholarship on pharmaceuticalisation?" The conceptual discussion now explains how these arguments link to the work of Abraham/Davis and Carpenter, and returns to these arguments in a more organised format in the discussion.

2.2 In addition, some introduction to pharmacogenetics/ genomics is needed as it cannot be assumed that all readers understand the basic aims of the science here.

I have added a definition in the introduction.

2.3 The conceptual framework was useful in setting-up the debate between Abraham/ Davis and Carpenter as a core argument that the paper addresses, but more needed to be done to develop this into a coherent framework. For example, the section on permissive regulation (page 7) comes to a rather abrupt end and needs better linkage with the following sections. The really interesting point about Jessop's view of the state needs further elaboration and linking to the notion of the 'translational state' which is touched on (too briefly) in later sections.. The key issues and tensions should be set-out at the end of this section.

Sadly Jessop has gone (one concept too many for a dense paper) but I have substantially rewritten the conceptual framework in the light of these comments.

2.4 The main body of the paper on the FDA and Pharmacogenomics is a useful account of the development of this emerging field of regulatory science which illustrates a number of important points and the author(s) demonstrate the way industry was involved in shaping policy. A little more about FDA's overall commitment to PGx would be useful.

I have not addressed this suggestion. I would respectfully invite the reviewer to consider whether the substantially rewritten paper still requires this particular addition. If so, I could put in a paragraph immediately preceding the discussion section.

2.5 The section on the Critical Path Initiative is also valuable, as this has become such a cornerstone of the agency's subsequent work. A little more detail of the Bush era critique of the agency would be useful here as background.

I think the detail the reviewer requests is now addressed by the historical exegesis in the conceptual framework/background section, albeit in a slightly broader historical timeframe which provides background on the role of Chicago School and the translation of their deregulatory agenda into policy during Reagan administration.

2.6 Finally, the section on Vioxx analyses the way in which the technology of PGx was framed as a solution to the problems raised by this landmark case. Whilst the analysis is insightful and develops the previous arguments, the use of evidence could be better. On Page 15/16 the paper is rather too dependent on extensive quotes from secondary sources. These could be cut back a bit and more narrative developed to explain their significance. The section also has a rather abrupt ending that doesn't either link back to previous sections or hint at future trends.

I have cut out several quotes and reworked the conclusion of this section.

2.7 The conclusion makes a series of valuable observations based on the data presented earlier. In particular, this highlights the changing nature of the FDA as part of a broader transformation of the state. However, whilst the technocratic shift and the influence of industry are evident in this story, the idea of the FDA becoming a neoliberal agency is not fully developed or evidenced, and more needs to be done throughout the paper to carefully do this in a way that is supported by the research findings.

The conceptual framework has been significantly reworked and the discussion now links back to that.

2.8 Furthermore, the point about the way in which pharmacogenetics reframes the problem of risk management (page 18; ln 36) is valid, but is not really the focus of the paper and is hard to follow given the lack of any real description of the technology. I think this should be cut.

I understand why the reviewer suggested cutting this section, but in fact I think it is central to main arguments of paper. I think that the problem with this section is the one the reviewer is more broadly concerned with which is about clear signalling of arguments in introduction and consistent development and reference back to them in the rest of the paper and a better articulation of how they are connected. The section has in fact been moved to the Vioxx section where hopefully its relevance is clearer (and also made clearer by the definition of pharmacogenomics now added to the introduction)

2.9 What is missing from the conclusion is an integration of the points raised in the conceptual framework and introduction. What does all this tell us about the debate between Abraham/ Davis and Carpenter? How does it support the claim made earlier about multiple actors shaping policy? How are ideas of pharmaceuticalisation relevant here and what is the link to expectations/ pharma futures?

I have substantially rewritten the discussion session to address these important criticisms.

In conclusion, this is a potentially valuable paper, the core of which is sound. It makes a series of important arguments that are of significance to debates in this area. However, the introduction and conclusion need reworking, and much better integration with the conceptual framing is required. If this were done it should be accepted.

Minor points

Page 4: Second quote needs referencing (ln22)

Page 5: Methods - this needs some further description e.g. details of the number of interviews and when conducted.

Page 8: The assumption that there was room for industry only (ln55) is not convincing. This needs rephrasing.

Page 11: The statement "this was a truly neoliberal FDA" (ln 32) is an exaggeration and cannot be supported by the evidence. Quotes on ln 50 & 55 need referencing. More needs to be done to sustain the claim of a neoliberal agenda at the FDA in the Bush era.

Page 15: Missing reference on ln12.

Page 16 & 17: Several missing references to quotes.

Page 17: Give full name for KBE first time used here

Make sure all abbreviations are introduced (PGx, PGt)

Use of different voices in the text need to be consistent - sometimes "I" and sometimes "we"