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Regulatory experiments and transnational networks: the governance of pharmacogenomics in Europe and the United States

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Abstract

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. Uncertainty about the regulatory standards and processes for this emergent technology have been widely cited as an obstacle to more widespread and rapid adoption of pharmacogenomics. Pharmacogenomics thus presents an ideal case study of the role of regulators in the co-production of new biomedical technologies. In this paper we describe the attempt to create a new transnational regulatory space for pharmacogenomics through the creation of novel regulatory experiments by an epistemic network encompassing regulatory agencies, academic scientists and industry. This process has been marked by the creation of new socio-technical spaces in the regulatory regimes for pharmaceuticals – a pre-regulatory space for the sharing of data outside the regulatory decision-making process and a pre-competitive space for the sharing of data between companies. It is marked also by the expansion of a transnational regulatory space for sharing data and setting standards across jurisdictional boundaries

Introduction

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 2006 Marisa Amati, head of the European Medicine Agency's Innovation Task Force addressed an industry conference in Paris. Her topic was the evolution of regulatory responses to the use of pharmacogenomics in drug development. She stated that in close collaboration with their

counterparts in the USA and Japan, the EMA intended to create transnational harmonized regulatory standards for this new technology *ex novo*. This was a bold ambition. Efforts to harmonise pharmaceutical regulation had been proceeding through the International Conference on Harmonisation (ICH) for 16 years, but this would be an attempt to build a harmonised regulation from scratch at the very inception of a new biomedical technology. Just as the technology of pharmacogenomics promised to transform the established system of pharmaceutical R&D, and revolutionise patient care, so too would it usher in a new era of regulation based on increased transnational cooperation and harmonisation.

Although the adoption of pharmacogenomics in the drug development process has been gradual, its use is growing rapidly. However, the adoption of such an approach presents a number of challenges for industry and regulators. It requires the pharmaceutical industry to abandon its preferred (and highly lucrative) block-buster drug model aimed at broad populations to one which is focused on more targeted populations and it is dependent on pharmaceutical companies developing new forms of collaboration with diagnostics companies (Hopkins et al, 2006). It also requires the elaboration of a clear regulatory pathway, one which combines the approval of therapeutics and diagnostics. Uncertainty about the regulatory standards and processes for this emergent technology have been widely cited as an obstacle to more widespread and rapid adoption of pharmacogenomics (Hogarth et al, 2006). Pharmacogenomics thus presents an ideal case study of the role of regulators in the co-production of new biomedical technologies.

There has been considerable political support for pharmacogenomics. For instance, the UK government's 2003 Genetics White Paper singled it out for its potential to provide early benefits from genetic research: "The greatest impact of genetics on healthcare in the shorter term is likely to come from pharmacogenetics …. New pharmaceutical products linked to a genetic test are likely to become available within the next five years." (DH: 4) Similarly, the European Union's Life Sciences and Biotechnology Strategy described a "paradigm shift in disease management towards both personalised and preventive medicine based on genetic predisposition, targeted screening, diagnosis, and innovative drug treatments." (EC 2002: 6) The international consensus on the promise of this new technology was apparent when the OECD agreed to carry out a programme of work investigating pharmacogenomics in 2004 as part of a broader programme on genetics and genomics.

This enthusiasm reflects the pervasive appeal of biotechnology to powerful actors in science, industry and government across the world. As Jassanof has noted, in Europe and the USA the birth

of a new bioeconomy was driven by "firm national commitments to basic science, economically powerful industries, and state authorities eager to demonstrate their support for a winning technology." (2005, p66) Such commitments are now integral to the economic strategies of the rising powers of Brazil, China, India and Singapore (Hogarth and Salter, 2010). Yet, as Jassanoff explains, in the case of GM crops, the universal appeal of the envisaged new bioeconomy led not to an international policy consensus on the regulation of biotechnology, but instead to radically different outcomes in the USA and Europe, consequent on fundamentally different framings of the technology. This paper will explore whether the construction of a regulatory zone for pharmacogenomics has also been marked by distinct differences in approach between the US and Europe.

The development of the contemporary bioeconomy is taking place within a dynamic of globalisation characterized both by a competition for national advantage and transnational cooperation to create harmonized regulatory frameworks. This paper is interested in exploring whether the globalisation of regulation weakens national sovereignty, the traditional source of authority and legitimacy for regulatory agencies, and instead empowers transnational epistemic networks of technocratic expertise; whose growth can be seen as "a transformation from representative democracy to indirect representative democracy" (Levi-Faur, 2005, p13). In comparing the US and Europe we will explore how the pursuit of similar policy goals to address issues which transcend national boundaries is shaped by local political factors, such as different approaches to risk regulation, organizational capacity and statutory authority.

International harmonization of pharmaceutical regulation

For much of the twentieth century the FDA set the global standard for pharmaceutical regulation, its structures processes and protocols helped to shape regulatory regimes across the world (Carpenter, 2010, p687). Since the early 1990s a new global dynamic has emerged in which the FDA has been partially eclipsed. The most comprehensive transnational harmonization of regulation has been achieved within the European Union. Since its creation in 1993 the power of the EMA has gradually increased. The scope of its authority has widened to encompass more disease areas, new types of innovative therapies and new phases in the regulatory cycle; it is "increasingly responsible for regulation of the risks and benefits of newly invented pharmaceutical products in Europe." (Davis and Abraham 2011, p414) However, EMA's growing power has not eclipsed that of national regulatory agencies, whose staff constitute the core expertise of EMA's key committees and who carry out the work of technical evaluation of new regulatory submissions. Thus, as Hauray and

Urfalino (2009) suggest, this process is best understood not as a process of Europeanisation but as the creation of a "European policy space" through a process of "mutual transformation" (432).

The regulators representing the world's largest pharmaceutical markets (USA, EU and Japan) have come together with their respective industry associations in a new forum, the International Conference on Harmonisation (ICH). A broader geographical constituency has observer status including Canada and the countries of the European Free Trade Assocation (EFTA), as well as the World Health Organisation (whose own efforts at harmonization predate ICH by several decades). Established in 1990, ICH has developed a series of guidelines on different aspects of pharmaceutical regulation which have then been adopted by its three member states (Abraham and Reed, 2001, p114) The stimulus for this process came from global competition for national advantage in the pharmaceutical market: in particular, the desire of first the US and then European governments to open up the Japanese market to their domestic pharmaceutical companies; and, within the European Union, an acceptance by member states that a harmonized EU regulatory system would assist European companies. Further justification for the process rested on the historic mission of pharmaceutical regulators to protect and promote public health, objectives which, it was argued, were better served by minimizing the cost of drug development and the delays in market access for new treatments which arose from the divergent standards and processes national regulatory agencies imposed on industry.(ibid,p 117)

Scholars agree that harmonization was driven by a desire to address industry concerns, and led to downward, rather than a ratcheting up towards the higher standards of the FDA, but they vary significantly in their judgements about the legitimacy of the process and whether it was beneficial. Opinon varies depending on whether authors view FDA's established approach was unduly precautionary. Thus Vogel (1998) welcomes harmonization reforms as a welcome jolt of efficiency, a view supported by Braithwaite and Drahos (2000, p394), whereas Abraham and Reed see them as a dangerous loosening of controls (2001). The important question of whether globalised pharmaceutical regulation represents the neoliberal defeat of the state by the market and the subordination of state power to the limited role of promoting business interests is beyond the scope of this paper but is instead the subject of a separate forthcoming paper.

As the ICH process began, the development of harmonisation within Europe shifted towards greater centralisation. In 1992 a new approach was established: a centralised procedure administered by the CPMP. This procedure was voluntary for most therapeutics, but it was

mandatory for biotech and other high technology products. This mirrored the earlier decision in 1986/7 when the new 'concertation' procedure (the first genuinely European regulatory approval process for pharmaceuticals) was established primarily for biotechnology products (Hauray and Urfalino, 2009 p437). There are a number of explanations for these decisions: the limited number of regulatory submissions in these high technology areas would ensure the new centralised system would not be overwhelmed in its early stages; there was a concern about a lack of biotechnology expertise amongst individual member states which necessitated a pooling of regulatory resources; and, finally the Commission believed that "it would be easier to harmonize standards that had not yet been created than to force states to change their existing ones" (Vogel, p5) New developments in biotechnology thus acted as an exogenous shock on the long-term dynamic of mutual transformation (Hauray and Urfalino, 2009, pp446-7) The growth of EMA's authority was thus, in part, predicated on the formation of an EU-wide epistemic community of biotechnology experts. This confluence of Europeanisation (and a broader transnational harmonisation) through the elaboration of new regulatory regimes for biotechnology recurs in this paper.

Method

My initial research in this area was conducted in 2006 as a result of a commission from Health Canada for an overview of global developments in the regulation of pharmacogenomics. The primary focus of this research was Europe and the United States (Japanese officials declined to participate in the research and there was no evidence of regulatory activity in other jurisdictions). 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

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 (Hopkins, et al 2007, Rose, 2006). However, biotechnology also generates social unease and public controversy, and has thus become the subject of political debate at the highest levels, as policymakers seek to balance the tension between managing public trust and realizing the clinical and commercial promise of genomic technologies. The management of these tensions has given rise to new modes of governance, in particular the rise of bioethics committees as mediators at the interface between science and society (Salter and Jones, 2002).

However, building trust in new biotechnologies is not simply a matter of managing public unease, it is also about addressing commercial uncertainty, and thus provides the regulatory agencies responsible for pharmaceutical drugs and medical devices with new challenges and responsibilities. Building trust is a fundamental part of the dynamic of technological co-production of new regulatory spaces by regulators, industry and other actors such as clinicians and academic scientists. In this case we explore the process of building trust in pharmacogenomic data, in the technologies which generate that data, and in the application of that data in regulatory decisions about clinical products. Following Millo and Lezaun, we suggest that in order to build trust in new technologies, regulators have to engage in regulatory experiments. Such experiments generate new knowledge about policy, allow regulators to test their capacity to handle new technologies and to gauge stakeholder reaction to their actions:

> By setting up an experimental space, where, for instance, they can unleash GM organisms or options contracts without making an irreversible commitment, regulators are able to assess their own capacity to cope with novel regulatory objects, and the reactions that the partial release provokes in relevant constituencies. (Millo and Lezaun, p188)

Much STS work on the regulation of novel biomedical technologies is focused on legislative processes and standard-setting, not least because this is where technologies may receive their first regulatory definition, and where some form of closure around issues of uncertainty is achieved. However, regulatory theorists have long advocated greater attention to implementation; to issues of enforcement and compliance (Hood, Rothstein and Baldwin, 2001, p15). Two recent STS studies of biomedical innovation which have taken this approach are Wilson-Kovacs et al's work on stem cell clinical trials (2009) and Abraham and Davis's work on non-steroidal anti-inflammatory drugs (2007).

The latter note that much STS work on new technologies fails to address implementation/enforcement, in part because they study technologies which are so immature they lack any regulatory interface or regime. They suggest that a more comprehensive account of the co-production of regulatory approaches to a new technology can be achieved by following it through its lifecycle from early-stage innovation through approval, marketing and withdrawal (p401). This paper attempts to do that for pharmacogenomics. To organise our account, we adopt a functional definition of regulation as encompassing three broad tasks: information gathering, standard setting and implementation (Hood et al, 2001, pp24-7).[1] In this case we suggest that these functions also have some utility as broad markers of the temporal stages in the emergence of a regulatory zone for pharmacogenomics (although the timing and processes of standard setting and implementation are more overlapping).

Phase one: information gathering - 2001-2004

Establishing a dialogue

Regulators' engagement with pharmacogenetics began with a process of information gathering, in which regulatory officials from EMA, FDA and PMDA organised conferences and workshops to discover more about how genomic data was being used by industry in drug development, and to explore how this data might be used in regulatory decision-making. (Goodsaid and Amati, 2010). The first such meeting was convened by the EMA in 2000 and brought together industry, academic scientists and patient groups. This led to an EMA consultation paper on terminology in pharmacogenetics (with initial input from industry) and the formation the following year of an ad hoc working group on pharmacogenetics which would be formally instituted as the Pharmacogenetics Working Party (PGWP) in 2005 (EMA, 2000).

The FDA held its first meeting in 2002, and even at this initial stage transnational cooperation was established - the FDA workshop was attended by Marisa Papaluca-Amati, then Deputy Head of Clinical Safety and Efficacy at EMA, who would become EMA's main champion for pharmacogenomics and who gave a presentation on European regulatory perspectives on pharmacogenetics. She stressed that even at this early stage EMA was operating on a global basis, working with the Council for International Organizations of Medical Sciences (CIOMS), a transnational NGO established by UNESCO and WHO whose activities span bioethics, health policy

[1] Hood et al use the term behaviour modification, rather than implementation but the other terms are theirs.

and drug development which had established its own working group on pharmacogenetics under the drug development and use programme.

As well as setting the tone for international co-operation, these events also established a new collaborative mode of engagement with industry, signaled by the fact that the workshops were co-chaired by Larry Lesko, Director of the Office of Clinical Pharmacology and Biopharmaceuticals at FDA and Ron Salerno, regulatory affairs Director at Wyeth. These two would go on to co-chair a further two meetings. In a media interview Lesko described the new collegial spirit which had been engendered:

> "In planning the workshop we have worked with a committee including many of these companies. I found the process of coming together around this workshop signaled a new openness and a new era." Lesko quoted in Branca, 2002

Even at this early stage we can observe the development of a transnational epistemic community, whose senior members, in both industry and agencies, would become vocal champions of pharmacogenomics. The collaborative nature of these workshops was itself a form of experiment, and like all experiments the data was published in scientific journals: reports of the meetings, co-authored by FDA officials and industry, were state-of-the-science review papers, summarizing the current status of pharmacogenomics and likely next steps. (Lesko and Woodcock, 2004)

Voluntary submission

The first FDA workshop confirmed that industry were concerned about how regulators might use the novel and complex pharmacogenomic data which firms were generating in their drug development programmes. As one FDA official told us: "Companies were very hesitant, they didn't know what FDA were going to do." (Interview, CDRH official, 2011). Senior FDA officials outlined industry concerns in more detail in a 2004 paper:

> The major concern was that the FDA would overreact to non-validated, exploratory genomic biomarkers, take them out of context, misinterpret them, cause delays in drug development, request additional clinical trials and/or put clinical trials on hold. This concern led to a reluctance of the industry to introduce genomic studies into their drug development plans. (Lesko and Woodcock, 2004, p766)

Regulators could only address these concerns by familiarising themselves with the kind of genomic data being collected by companies, but with no certainty about how such data might affect the approval process, companies were reluctant to open it to scrutiny. The solution to this Mexican stand-off was the creation of a new kind of pre-regulatory space: a 'safe harbour' for genomic data termed the Voluntary Genomic Data Submission (VGDS). First mooted by FDA at the their 2002 workshop, VGDS programmes were initiated in the USA and Europe with the publication of draft guidance documents in 2003 (EMA, 2003 and FDA, 2003).

This new pre-regulatory space was significant – it was the first time that industry had been invited to share exploratory data on a voluntary basis outside the formal approval system. Like the workshops it signaled a new more open and informal mode of interaction with industry. The following year Janet Woodcock described the intent at an FDA advisory committee meeting:

> ...FDA must provide the regulatory framework and some reassurance as we move forward that individuals and firms are not going to be punished for this, so to speak. And the pharmacogenomic guidance that we published the draft last year is an example of that. It provides a space, an experimental space, where those tests can be done without the fear of all these regulatory consequences occurring and where the information can be shared. (Woodcock, in FDA (2004) p68)

The experimental nature of this space was a little less clear cut in Europe. Although broadly similar to the FDA process, the EMA system of Briefing Meetings had less of a strict delineation between the voluntary submission and any ensuing formal submission, since PGWP members who participate in briefings meetings were also likely to be involved in any subsequent evaluation for approval. However, the processes were sufficiently similar in essentials and intent to allow FDA and EMA to institute a mechanism for bilateral VGDS/briefing meetings where they would review data together.

As well as signaling a new mode of engagement with industry, the VGDS necessitated new networks of regulatory expertise. At FDA VGDS are handled by the Interdisciplinary Pharmacogenomics Review Group (IPRG) which was formed to bring together staff from the devices and drugs sections of the FDA. It is the primary review body for Voluntary Genomic Data Submissions (VGDS) but it can also play a role in the review of formal product submissions. Its inaugural membership included senior FDA officials such as Janet Woodcock, Larry Lesko and Steve

Gutman (Director of the Office of In Vitro Diagnostics (OIVD)) and it was chaired by Felix Frueh, Associate Director for Genomics in the OCPB. EMA's ad hoc Working Group on Pharmacogenomics (which would eventually become the PharmcageneticsWorking Party (PGWP)) similarly brought together expertise from across the agency and its network of scientific reviewers. However, the membership of EMA's group was broader, reflecting the EMA's constitution as an EU-wide network of regulatory officials from member state agencies and other experts. The PGWP is thus made up of an equal number of regulatory scientists and academic scientists with expertise in the evaluation of medicines and devices.

Regulators and industry both have reported satisfaction with this process (Interviews with FDA/EMA officials and industry, 2006/2011). A joint paper by EMA and FDA in 2010 reported that the FDA had reviewed about 40 voluntary PG data submission and that EMA had held more than 20 briefing meetings, and more recently formed Pharamcogenomcs Discussion Group in Japan had held about 10 informal meetings with industry to discuss the use of genomic data in clinical trials (Goodsaid and Amati, 2010). In addition, FDA and EMEA have held four bilateral VGDS/briefing meetings. At a joint meeting in 2007 the PMDA also participated as an observer. Commenting on their joint meetings, Felix Frueh suggested that the FDA and the EMA shared a very similar approach to the science, differing only in their administrative procedures (cited in Anonymous, 2006), a phenomenon which he subsequently described as "Global science, local regulations" (Goodsaid and Frueh, 2006).

By the end of this initial phase, the FDA and EMEA had both emerged as champions of pharmacogenomics as an exemplar for novel approaches to drug development. This was made clear in 2004 when pharmacogenomics was put in a new policy context. In a striking example of policy synchronisation both agencies released wide-ranging reports which positioned pharmacogenomics at the heart of a broader regulatory reform agenda. FDA's Critical Path initiative (2004) and EMEA's Roadmap (2004) both 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. The solution that both agencies proposed was research and innovation to create a new "product development toolkit", a greater emphasis on translational research for the enhanced use of novel biomarkers in drug development, diagnosis and screening, and the review of existing clinical trial design and statistical tools for drug evaluation. Both agencies suggested that as regulators they were in a unique position to facilitate the transformation they proposed. The agenda which these reports set out was one which would

require new forms of collaboration between regulator, industry and academic scientists in order to set new regulatory standards for the development of medical products. This new phase would bring new forms of transnational cooperation and create new experimental regulatory spaces.

Phase two: pharmacogenomic standard setting

In the first phase regulators were engaged in gathering data, in the second phase, they moved on to processes which would ensure that pharmacogenomic data was trustworthy when it was used in regulatory decision-making. This required the elaboration of standards, processes and collaborative programmes for validating genomic data and involved new forms of collaboration with industry but also a greater level of engagement with academic scientists. Despite its scientific ambitions FDA has only very limited resources to fund research, so the pursuit of its Critical Path agenda has involved joint projects with industry, academia, and other HHS agencies such as the National Cancer Institute (NCI) and the Centers for Medicare and Medicaid Services. To provide a new platform for its activities, the FDA has been one of the founding partners of the Critical Path Institute (C-Path) established by the University of Arizona and Stanford Research Institute International. Supported by, but independent of, the FDA, the C-Path was another new space for regulatory experiments with pharmacogenomic data. Whereas VGDS had created a pre-regulatory space, C-Path would help to foster pre-competitive spaces in which industry collaborated on validating genomic biomarkers.

A qualified success: approving biomarkers

Amongst its initial projects was the Predictive Safety Testing Consortium (PSTC), a public-private collaboration for validation of toxicogenomic renal biomarkers which signal kidney injury and thus could be used to identify safety issues at the initial stage of drug development. The project was in part a response to the fact that the FDA had been receiving toxicogenomic data from different companies, all using different markers. The agency suggested the companies pool their data to identify the best methods and markers. The EMA joined the initiative and the data was reviewed jointly by both agencies. In 2008, the FDA and the EMA announced that they had reviewed and accepted seven new biomarkers in a bilateral VGDS; cooperation had moved beyond sharing data to establishing joint standards and the VGDS which had begun as a pre-regulatory experimental space had now taken on a quasi-regulatory function. The project was significant for its elaboration of a pathway for approval of a genomic biomarker, and the clarification of some of the evidentiary and experimental issues. It also provided another forum for the consolidation of the pharmacogenomics epistemic community, bringing together scientists from the FDA and the EMA with researchers from

17 biopharmaceutical companies, four academic institutions, and the Critical Path Institute (Anonymous, 2010, p431). The project was hailed as a landmark in fostering public-private, transnational and inter-firm collaboration:

> ... co-operative relationships between regulators and drug companies are a relatively new development. Pan-industry research collaborations are also new ... the PSTC shows how open and cooperative precompetitive research among large pharmaceutical companies can benefit the entire industry. (NBT 2010 editorial, p431)

The data from the project, and the administrative protocols which managed the collaboration, were described in a series of articles in Nature Biotechnology in 2010. An accompanying editorial feted the project as a landmark in bilateral regulatory collaboration: "the first ever cooperative decision by the FDA and EMA made on the basis of a joint data submission" (Anonymous, 2010, p431). A joint commentary by Frederico Goodsaid, the FDA's associate director for operations in genomics, and the EMA's Marisa Amati described their joint accomplishment:

> At the international level, the joint activities of the EMEA Pharmacogenomics Working Party and the FDA Interdisciplinary Pharmacogenomics Review Group have established a working model for global regulatory review of exploratory biomarker data. On this basis, and in view of the advances in the field, the regulatory agencies have developed dedicated processes to deal with biomarker qualification. These biomarker qualification processes address the need of individual organizations and consortia asking for a regulatory qualification of the results obtained from the ongoing collaborative efforts. Such a path
> has been tested in these biomarker qualifications.

Noteworthy here is the idea that FDA-EMA bilateral cooperation establishes the framework for a global model for biomarker qualification. In fact a global harmonisation initiative in this area began in the ICH forum in 2008, after the PTSC project was underway (Goodsaid and Amati, 2010, p442). The chronology suggests that if the PTSC project was, as indicated by participants, a landmark in biomarker qualification, it would seem that the impetus for transnational harmonisation is largely coming from this transatlantic partnership between the US and European agencies. The third member of ICH, Japan's PDMA, thus appears to have a largely subordinate role. Moreover, the project also suggests that FDA are the dominant partner in the bilateral partnership with the EMA: the PTSC was an FDA/C-Path initiative which the EMA was invited to join, the majority of PTSC

members were US-based, FDA laboratories were the site for some of the PTSC experiments and it was the FDA's Goodsaid who was lead author on the joint paper with the EMA's Amati.

The global competition for pre-competitive space

The development of new pre-regulatory/pre-competitve spaces was marked by both cooperation and competition between agencies. FDA Commissioner Margaret Hamburg has recently cited international competition as a justification for enhanced funding of FDA regulatory science work, in a statement which makes a confident assertion of the USA's current hegemonic status:

> "Without question we face formidable competition overseas, especially from Europe and China, where significant investments are being made in regulatory science. But the FDA remains the regulatory gold standard throughout the world." (Hamburg, WSJ, 2011)

These sentiments were a transatlantic echo of arguments made by the European pharmaceutical industry trade body EFFPIA when it lobbied for EU funding for the Innovative Medicines Initiative (IMI), a new Joint Technology Platform to pursue pre-competitive research. EFFPIA identified Critical Path-inspired initiatives in the US such as the PSTC and the Biomarkers Consortium as global rivals:

> the topics of research have been agreed upon globally i.e. improving the prediction of safety and efficacy evaluation. This situation has created a global competition to attract private investment in pre-competitive frameworks that are taking place across the world … Should Europe decide not to invest in IMI, such pre-competitive pharmaceutical research projects (and the associated pharmaceutical R&D investment) are very likely to take place outside Europe … [and] Europe's biomedical base will decline … result[ing] in further re-location of the biopharmaceutical industry's R&D capabilities outside Europe. (EFFPIA/IMI, 2006, p11)

Thus, whilst the new Critical Path / Road Map agenda fostered collaboration, the inception of C-Path and its European counterpart (the Innovative Medicines Intiative (IMI) in part reflected a determination to gain competitive advantage in the global bioeconomy. The EFFPIA/IMI document argued that the advancement of regulatory science necessitated an EU-wide approach to leverage collective resources and to avoid a fragmented approach:

> As the majority of medicines are approved through the centralized European procedure, application to European rather than national regulation and guidance is essential if the IMI is to impact drug discovery and development. Action at a national level would be limited in terms of the industrial and academic scientific expertise available in any one country. (EFFPIA/IMI, 2006, p8)

Just as EMA argued for global harmonization *ex novo*, so European industry argued for a harmonized approach within the EU, thus reinforcing the growing authority of EMA in this emerging regulatory space. However, compared with the FDA's intimate relationship with C-Path, EMA has adopted a more arm's length relationship with IMI. Janet Woodcock sits on C-Path's Board of Directors as an advisory liaison, but EMA officials sit on neither the IMI's governing board nor its scientific committee. A statement by EMA in 2009 indicates a willingness to provide input to IMI projects but highlights the potential for conflict of interest in developing technologies which might be relevant to formal regulatory approval processes. The statement seems puzzling since IMI is dedicated to precisely the kind of pre-competitive research which EMA participated in as part of the PTSC project. Compare this attitude to the following statement about the FDA's Critical Path initiative:

> A key component of Critical Path Research is the participation and critical evaluations of the very regulatory scientists who will later rely on the results obtained with these new tools as they are applied to the development of new pharmaceuticals. (Mattes et al, 2010, p433)

At issue seems to be a difference between the two agencies in their approach to the dividing line between pre-regulatory, pre-competitive space and the formal space of regulatory product approval. The EMA 2009 statement cites limitation of resources as another reason for its selective approach to IMI collaborations. This is the converse of FDA's argument that finite resources necessitate collaboration. This difference may stem in large part from the fact that FDA, its limited research resources notwithstanding, is a far larger agency than EMA. Of course the European regulator can draw on its extensive network of member state regulatory officials and academic scientists who carry out much of EMA's work, but EMA's statement, taken at face value, suggests that there are limits to this approach. A member of the PGWP confirmed that resources were a limitation:

> EMEA are short-staffed and cannot do everything at the same time, so we focus on the most urgent things, like gene therapies … We have the PGWP which is doing very well by meeting three to four times a year; FDA's IPRG have 20 full-time people. It is just not on the same scale. (Interview with PGWP member, 2006)

The question of scale is amply demonstrated by the discrepancy in VGDS/briefing activity - as noted earlier, FDA had performed twice as many such sessions: 40 VGDS to EMA's 20 briefing meetings. This statement also reveals a certain scepticism about the relative importance of pharmacogenomics as a regulatory issue even within the PGWP, striking a tone which is quite different to FDA's IPRG and which, as we shall see in the next section, extends to formal regulatory decisions made by the agencies. However, our interviews suggested that this skepticism is not institutional but instead reflects differences in attitude between leading members of the PGWP (FDA interview 2006, industry interview 2011).

At the same time as these standard setting initiatives were underway, regulatory agencies were implementing pharmacogenomics in new product approvals and through the relabeling of existing products. This activity brought pharmacogenomics out of an experimental space into the real world putting it to new tests.

Phase three: implementation

Introducing a genomic way of thinking – FDA's relabeling strategy

The existing pharmacopeia contains many drugs whose safety and effectiveness is in some degree affected by inter-individual genomic variation. Gathering such pharmacogenomic data and communicating it to doctors and patients via the labels of approved drugs is a central part of the FDA's strategy for the promotion of pharmacogenomics (Lesko, 2005). As an artice in the New England Journal of Medicine described their activity: "In recent years, the FDA has aggressively pursued drug-label modification when excess risk can be convincingly linked to a genetic marker." (Wang et al, 2011) Relabelling decisions and recommendations have been made for a number of drugs including the anti-depressant Straterra, and the blood-thinning drug warfarin. However, labelling updates have generally been advisory/cautionary rather than mandatory, reflecting the limitations of the clinical data available to support the use of a test. For instance, the colorectal cancer drug irintotecan (Campostar, Pfizer) was relabelled by FDA after growing evidence that severe adverse events in some patients were associated with a specific allele of the UGT1A1 gene.

Whilst there was insufficient data to make precise dosing recommendations, it was felt that the data on a heightened risk of neutropenia was sufficiently strong to justify relabelling.

A member of the EMA's PGWP questioned FDA's relabeling of Irinotecan, saying he was "not sure they had all the data they needed, maybe FDA are more enthusiastic, the dossier is not absolutely compelling." (2006 interview). Official confirmation of this view came in a 2008 EMA reflection paper on pharmacogenomics in oncology, which stated that the PGWP found the data on UGT1A1 "suggestive" but "insufficient": "the positive predictive value (~50%) was considered too low for inclusion of definitive statements in the product literature." (2008, p7) Some measure of disagreement on specific regulatory decisions are inevitable, but the Irinotencan/UGT1A1 decision was just one of many drugs relabeled by the FDA to include pharmacogenomics data, which have not been replicated by the EMA. The relabeling of existing drugs is an area where there is a clear difference between Europe and the USA. European regulators have been far more reluctant to relabel than their US counterparts. One EMA official expressed sympathy for what they described as the FDA's efforts to "introduce a genomic way of thinking" through relabeling, but suggested that the EMA was adopting a stricter approach: "For us relabeling requires very compelling evidence that modifies the risk-benefit analysis." (EMA staff interview, 2006) In a presentation to the Clinical Pharmacology subcommittee in 2004 Janet Woodcock, then FDA's Chief Medical Officer described a rather different attitude. The architect of the Critical Path intiative and the agency's most senior pharmacogenomics champion suggested that regulators must wean themselves off a reliance on binary yes/no decisions about the safety and efficacy of drugs, in favour of a model of drug development (and regulation) as the "progressive reduction of uncertainty". Biomarkers, she argued, could help to reduce uncertainty, but in order to adopt them regulators must accept that biomarkers themselves were also a source of uncertainty, an uncertainty which would only be reduced through their use in medical practice:

> ... biomarkers have to be used to be accepted ... part of understanding the performance of these newer technologies is to use them, to see how they move with treatment or how they fail to move with successful intervention, to see how they perform in various populations and with a wide variety of drug interventions ... (Woodcock in FDA (2004) p66)

It would seem that for the FDA's most senior champion of pharmacogenomics, relabeling was a real-world regulatory experiment, a process of trial and error in which the drug label itself had become an experimental space. For EMA the delineation between the space of regulatory

experiment and the space of regulatory decision-making was far more clear-cut. Perhaps unsurprisingly, this difference in attitudes extended to disagreement about the types of evidence which were acceptable for relabeling decisions. In an editorial discussing new scientific data to support their decision to relabel warfarin Lesko and Woodcock addressed a question which had become increasingly controversial in the USA as the FDA increased its pharmacogenomics relabeling activities:

> "In some cases, randomized, controlled trials will be needed to determine whether pharmacogenetic testing is worthwhile; in others, less rigorous approaches will suffice. Given the expected volume of genetic information and the relative paucity of randomized, controlled trials involving marketed drugs, we need clear thinking about what is required for the adoption of pharmacogenetic testing." (2009, p)

The previous year EMA had expressed less willingness to accept such observational data:

> "From the regulatory point of view, the associations highlighted above will need to be robust and validated. Observational studies /data or association studies alone may not be adequate to provide a basis for a regulatory action such as inclusion of PG information in the product literature (SPC/label)." (EMA, 2008 p8)

However, this is more than an epistemological divide; there are also institutional differences which preclude a common EU/US approach. The EMA's 2008 reflection paper notes a number of recent scientific findings which are of "scientific importance" including the role of CYP2D6 genes in modifying response to the breast cancer drug tamoxifen and the role of TPMT genes in modfying response to the drug mercaptopurine in treatment of acute lymphatic leukemia. However, the EMA noted that both drugs had originally been approved nationally not through the centralized procedure, and therefore relabeling is beyond the agency's jurisdiction: "These matters concerning medicinal products approved nationally are discussed at the level of the National Competent Authorities in the member states." (EMA, 2008, p7)

A legal void: (not) approving diagnostics

This is not the only area where EMA currently lacks regulatory authority over the use of pharmacogenomics in the real-world setting. Unlike the FDA, the EMA has no statutory power over the diagnostic tests which are central to pharmacogenomics in clinical practice (Hopkins 2006,

Hogarth, 2006). In the USA, the Food Drugs and Cosmetics Act covers both drugs and diagnostics (which in regulatory terms are a form of medical device). This is not the case in the EU where medical devices are governed through three separate directives and responsibility rests entirely at member state level (Altenstetter and Permanand, 2007). The EMA reflection paper on co-development of drugs and diagnostics (2010) states that: "The legal requirements for IVDs or other medical devices are outside the scope of this paper and are addressed in other relevant legislation and guidelines." (p3) The FDA guidance makes explicit that in the case of co-development then tests are approved under the FDA's legal authority over medical devices and the drugs under the FDA's legal authority over drugs. It is not clear from the EMA document what legal authority it has over companion diagnostics nor whether the agency intends to recommend or mandate the use of particular medical devices, although much of the guidance is about assay validation. The FDA guidance makes clear that a companion diagnostic must be FDA-approved in order to appear on the drug label, and that drugs should only be approved (or relabelled to include recommendations for use of a companion diagnostic) if there is an approved diagnostic (FDA, 2011b). At the 2006 European meeting of the Drug Information Association in Paris Eric Abadie, Chair of the PGWP, stated that it was not possible to make an explicit reference to a relevant IVD test in the labelling for drugs.

At the same meeting Abadie described the EU IVD Directive as a "legal void", because it does not mandate a requirement to demonstrate the clinical validity of new diagnostic tests, a statement which refers to some profound differences in approach between the USA's regulatory regime for IVD devices and that of the EU (Hogarth, 2006). Firstly, the FDA subjects new tests, including pharmacogenomic tests to a risk-based system of pre-market scrutiny and approval, whereas in the EU most diagnostic tests (including pharmacogenomic tests) are self-certified by the manufacturer, who is the only party to assess whether the device complies with the regulations. Secondly, the FDA evaluates both the accuracy of a test in identifying a biomarker (analytic validity), and the clinical relevance of that biomarker as a measure of disease status or, in the case of pharmacogenomics, drug response (clinical validity). In the EU there is ambiguity and disagreement amongst member states on this last point, with the most common interpretation being that the Directive requires evidence only on analytic validity (Hogarth et al, 2007). On this interpretation, the EU regulatory regime is entirely inadequate as a legal mechanism for the type of biomarker qualification standards and processes which EMA has painstakingly elaborated in collaboration with FDA.

The European Commission has initiated a process of revision for all the medical device directives and has singled out the IVD Directive for special attention (EC, 2008 and 2010) Amongst its proposals are some kind of role for the EMA in the regulation of high-risk devices, and a new classification system for IVD devices which would mean that many more tests (including pharmacogenomic tests) would be subject to independent pre-market evaluation. The latter suggestion is broadly welcomed, but an enhanced role for EMA has more limited support and significant opposition from industry and some member states. The very gradual process by which a centralised EU system for pharmaceuticals emerged, suggests that resolution of these issues may take at least a decade.

This difference in statutory authority has implications for transnational harmonisation: FDA officials in the Office of In Vitro Diagnostics (OIVD) which regulates laboratory tests, including pharmacogenomic tests, as medical devices report that they have had little contact with European colleagues, in large part because there is no EU equivalent of the OIVD to interact with, an observation that confirms the central role which the EMA plays in facilitating transnational harmonisation (FDA interviews, 2006, 2011). There is an ICH equivalent for medical devices – the Global Harmonisation Task Force (GHTF) – and in recent years it has been carrying out a specific programme of work on IVD devices. However, FDA have until now treated the GHTF process as largely "aspirational" (FDA official personal communication 2010). One OIVD official stated that that this was because "our statutory mandate doesn't fit" with the regulatory model elaborated by GHTF: "we've become accustomed to standing alone" (FDA interview, 2011). Perhaps unsurprisingly, there has been no formal discussion of pharmacogenomics in this forum thus far.

Discussion

The emergence of pharmacogenomics exemplifies the central role played by regulatory agencies in the co-production of new healthcare technologies. Regulatory agencies and regulated firms each now contain pharmacogenomics champions and an organisational infrastructure dedicated to the application of this science in development and evaluation of new drugs. These individuals may be said to comprise an epistemic community defined by their common interest in the promotion of pharmacogenomics. On the one hand regulators are adjusting their systems to take into account the new technologies being adopted by industry, and on the other hand the regulatory agencies are steering the adoption of pharmacogenomics through a range of initiatives including: organisational restructuring; the establishment of new mechanisms for voluntary sharing of genomic data outside the formal approval process; the development of guidance on regulatory

processes and types of data needed, all taking place in the context of international co-operation and harmonisation.

Pharmacogenomics is marked by the creation of new socio-technical spaces in the regulatory regimes for pharmaceuticals – a pre-regulatory space for the sharing of data outside the regulatory decision-making process and a pre-competitive space for the sharing of data between companies. It is marked also by the expansion of a transnational regulatory space for sharing data and setting standards across national/regional jurisdictional boundaries. However, the significance of these new socio-technical spaces should not be overstated; they have increased the complexity of the regulatory regime but they have not transformed it: the cooperative nature of initiatives such as CPI and IMI has not undermined the competitive nature of the pharmaceutical industry; nor has the increase in transnational cooperation effaced national longstanding differences in regulatory regimes (or efforts by staff to position their respective agency as leaders); and the creation of a transnational space in pharmacogenomics has only been possible because of a well-established dynamic of harmonisation, bi-lateral and multi-lateral co-operation between agencies. To this latter point, it should be noted that where the transnational harmonisation dynamic is far weaker (in medical devices) then the creation of a transnational pharmacogenomics regime has not occurred.

Pharmacogenomics has not repeated the example of GM crops, where the universal appeal of the envisaged new bioeconomy failed to impel an international policy consensus on the regulation of biotechnology. There are clear differences between the USA and Europe, most notably in the policy of relabeling, but for the most part there has been a broad and powerful alignment of activities, through bilateral cooperation and ICH-based activity. Thus far pharmacogenomics has not generated controversy amongst the general public, and expert disagreement has largely been restricted to specific product decisions, not the platform technology.

The emerging regulatory regime for pharmacogenomics is reinforcing the transnational harmonization of pharmaceutical regulation. The fact that the EMA has taken the lead in defining the regulatory approach to pharmacogenomics within Europe is indicative of the agency's growing power and confirms that the dynamic of Europeanisation is in part propelled by EMA's role in establishing regulatory frameworks for new forms of biotechnology. Its actions are in turn dependent on processes of bilateral cooperation with the FDA and harmonization through ICH. The example of pharmacogenomics would seem to confirm that global epistemic networks of

technocratic expertise are becoming more important as a source of regulatory authority in pharmaceutical regulation.

The differences between EMA and FDA become more apparent as we move from standard setting to the level of implementation. The issue of relabeling reveals profound disagreements about the types of study and amounts of data required to justify the use of pharmacogenetic testing to tailor drug dosing. There is a clear parallel here with the findings of Davis and Abraham's comparative study of risk management strategies in the USA and EU (2011). The parallel is pertinent because pharmacogenomics relabeling is itself a risk management strategy. Acknowledging what Demortain describes as 'cognitive alignment' between the USA and Europe in setting standards for risk management, Davis and Abraham demonstrate that the FDA and EMA diverge widely in their implementation of risk management, with the US agency far more likely to use risk communication strategies to maintain drugs with serious adverse effect risks on the market, and the EMA more likely to withdraw such products. Although the drugs which have been relabelled are not ones which EMA have withdrawn, the divergence in pharmacogenomics relabeling would appear to confirm a greater US propensity to adopt risk management strategies.

Although these are in large part disagreements about evidence standards, the fact that they occur in the context of enforcement activity rather than in the elaboration of guidance would appear to confirm Braithwaite and Drahos' argument that globalisation of regulations is primarily about setting standards, norms and principles, rather than implementing them; enforcement remains a local responsibility (2000, p10). This is the case within the EU as well: the EMA has successfully asserted its authority to lead the development of an EU-wide regulatory regime for pharmacogenomics conceptually in terms of the elaboration of standards but it has only partial implementation powers; its authority is limited by the dual nature of the centralized/decentralized regime for pharmaceutical regulation which prevents it from relabeling drugs which have been approved under the decentralized procedure.

EMA is hampered by other constraints in its attempt to develop the EU's regulatory regime for pharmacogenomics. Unlike FDA and PDMA it lacks any legal authority in the approval of diagnostic devices, but perhaps more important is that the European agency clearly far less resources than its larger US counterpart. Thus the pharmacogenomics case would appear to support the general observation that the US state is the actor with the greatest influence on the globalisation of regulation (Braithwaite and Drahos, p475) and Carpenter's assertion of the hegemonic status of the

FDA in setting the foundational conceptual terms of pharmaceutical regulation globally (2010, p686-726). However, it also confirms that the FDA's power is now underpinned by collaborative participation in global of harmonisation. The established nature of that globalising trend in pharmaceutical regulation can in part explain the dynamic we have outlined here but in itself seems an insufficient explanation for the scale and pace of activity in the case of pharmacogenomics, which would appear to confirm the power of biotechnology to operate as an exogenous shock on transnational harmonisation (Hauray and Urfalino, 2009). But to stop there would be to rely on technological determinism as an explanation for this dynamic, an unsatisfactory account of the political dynamics of this socio-technical regime. Macey (2003) suggests that understanding the globalisation of regulation requires attention to the motivations of regulatory bureaucrats in furthering their institutional interests, and that there are three circumstances in which regulators might push for globalisation:

> "in order to permit regulators to act in a cartel-like fashion, so as to prevent regulatory arbitrage, which occurs when firms migrate to foreign jurisdictions to avoid the grasp of a domestic regulator ("regulatory carterlization"); (2) in circumstances where governmental actors or regulators can increase their power by persuading or forcing other countries to adopt regulations favoured by the first country ("regulatory imperialism"); and (3) in circumstances where an administrative agency lacks domestic support for a favoured policy, and uses regulatory globalization to make it more difficult for local political rivals to block that policy."(1353-4)

The same process of globalisation may be supported for different reasons by different countries depending on the local circumstances. We might suggest that there is a mixture of motives in the case of pharmacogenomics. The competition amongst nations to host pharmaceutical R&D activity generates anxiety about reform of the rules governing such work. The power of the pharma industry's lobby in major pharmaceutical markets like the US and EU means that regulators desire to implement reform might best be pursued through cooperative efforts in order to avoid domestic political opposition. Whilst much STS work on the governance of novel technologies focuses on regulation as a response to perceived risk, what we observe in the case of pharmacogenomics is novel technology creating an opportunity for the expansion of regulatory authority, in particular what Capenter terms conceptual power. This is perhaps most notable in relation to EMA, where its ability to orchestrate a unified European response to pharmacogenomics has further bolstered its growing authority as the de facto regulator for novel biomedical technologies within the European

Union. If we can understand the adoption of pharmacogenomics as an effort to expand regulatory power into the genomic space, then it is in the interests of the agencies who wish to pursue that goal to do so together. This is regulatory imperialism, not in terms of one national agency imposing standards on its counterpart in other countries, but a collective of agencies imposing standards on other actors within their regulatory space.

The prudence of this 'safety in numbers' strategy stems from regulators' relative inexperience with genomic science, a naiveté which heightens the risk of policy errors and thus poses a risk to regulatory reputations. This model accords with Mikler's recent argument that regulatory globalisation may not be a zero-sum game; that states may find it in their interests to share sovereignty "between states, as well as between states and other actors", in order to create effective regulation and to extend their influence beyond their own borders (2008). If Pharmacogenomics is a regulatory experiment then this is also a question of 'trust in numbers', the need for "mechanisms for generating a more robust consensus around particular policy options." (Millo and Lezaun, p179). Janet Woodcock described the VGDS process as an experimental space where industry could share data "without fear of punishment"; this latitude worked both ways, serving to insulate regulators from accusations of precipitative action. The transnational networks which performed these regulatory experiments were themselves tests of new modes of collaborative governance. As pharmacogenomics becomes more established in drug development and evaluation, we will be able to better understand whether convergence or divergence most accurately characterises the implementation of this emerging regulatory zone in regulatory decision-making. Just as biomarkers must prove themselves in clinical application, so the true test for transnational harmonisation *ex novo* will be its impact in the real-world setting of regulatory approval.

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