

# **Comparing Medicine Regulation**

## **The Vioxx Crisis and its Effects in the UK and the US**

Mette Marie Roslyng  
King's Centre for Risk Management  
King's College London  
Strand, London, WC2R 2LS  
Tel: 44+(0)2078-481217  
Email: [mettemarie.roslyng@kcl.ac.uk](mailto:mettemarie.roslyng@kcl.ac.uk)

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### **Abstract:**

The withdrawal by the pharmaceutical company Merck, on September 30<sup>th</sup> 2004, of their anti-inflammatory drug Vioxx placed drug safety and the role of pharmaceutical companies firmly on the political agenda. Vioxx became a landmark case in the new focus on poor risk communication, diminished trust and regulatory failings in the area of drug safety. Moreover, the case clearly shows the limitations of adopting a risk elimination approach in risk studies, due to the nature of drug safety in general, where any side effects must be considered in the light of the usefulness of the drug.

The paper examines how the regulatory systems in the UK and the US dealt with a crisis where drug safety came under public and political scrutiny and how the Vioxx case, furthermore, caused certain fundamental changes in risk regulation regimes in the pharmaceutical area. On a theoretical level, the paper examines how current approaches to regulation can further the understanding of a regulatory crisis, particularly evaluating the core assumption of regime theory and network theory in this light. When comparing the regulatory regimes in the US and the UK and the challenges they are facing, the general insight that regulation is failing is discussed in the light of the implications for the health authorities. This, furthermore, brings forward considerations on the relations between the authorities, the stakeholders and the political actors and the degree of co-operation and conflict existing between them. The changes in the risk regulation regimes are particularly considered in relation to a situation where risk is controversial and political in the light of a high level of public debate.

## **Introduction**

When Merck withdrew their best-selling painkiller Vioxx from the market in September 2004, it happened on the background of a number of media news stories, scientific studies and general scepticism over the safety of the drug that seemed to lead to an increased risk of heart disease and stroke in some patients. As with many new drugs, there were great hopes for the Cox-2-inhibiting group of anti-inflammatory drugs, which included Vioxx. Unlike existing painkillers, the Cox-2s did not seem to carry the common side effects of bleeding and stomach ulcers and, as such, they were marketed as a less risky alternative to other non-steroidal anti-inflammatory drugs (NSAIDS). However, it turned out that with some likelihood the Cox-2 enzyme had a beneficial effect on blood clotting, so that with the use of a Cox-2 inhibiting drug, the patient would lose this effect.

On the 18<sup>th</sup> November 2004 the US Senate Finance Committee conducted a hearing to look into the Food and Drug Administration (FDA) and the pharmaceutical company Merck's role in the possible mismanagement of the safety of the painkiller Vioxx. This was, for some critics, a rather belated reaction to a problem with drug safety that the FDA could have given more critical consideration. They believe there is evidence that the FDA certainly knew about the increased coronary risk, but chose to ignore it. The Vioxx scandal led in the US to accusations that the FDA failed the patient and acted in the interest of industry (Giles 2004). The Vioxx case can be seen as significant event that highlights some of the inherent weaknesses and failings in the regulatory system as it was at the time. The scandal therefore caused a re-orientation and a strengthening of regulatory structures that this paper will explore. In the UK, likewise, the Committee on Safety of Medicines (CSM) considered the original trial data from the Merck study VIGOR to indicate that Vioxx and the Cox-2s did not constitute a coronary health risk and, like the FDA, the Committee was caught unaware by the Merck withdrawal in September 2004. This also resulted in criticism of the authorities albeit less vigorously than in the US.

The area of drug safety raises some particular questions and challenges for the regulatory regime. First of all is it an area of intense conflict over competing interests where several

stakeholders attempt to define what is in ‘the patient’s interest’. Secondly, the regulating agencies face the challenge of regulating a field dominated by highly complex and contestable science. How can regulation be based on ‘best available science’ when this concept can seem unclear and difficult to obtain? The area of drug safety demands particular attention to risk regulation as few drugs are without any side effects, thus leading to a difficulty in assessing risk and ensuring the patient. Certain side-effects may also be acceptable considered against the benefit the drug can bring to seriously ill patients. Randomised clinical trials are designed to determine the efficiency of a drug compared to either placebo or existing medicines (does it work?) and whether it has any side effects. The existing regulatory system, in principle, relies on the results from these drug trials to make decisions based on risk versus benefits of a drug. However, the Vioxx scandal reveals how the existing regulatory system comes under attack for being unable to ensure public health using these principles. This points towards some systemic failures and a need for a reform of drug regulation and a rethinking of how the stakeholders relate to the public authorities as well as how private interests are accused of influencing drug regulation on the expense of public health interests. How can we conceptualise these accusations and thus acquire a more developed understanding of regulatory reform in the area of medicine regulation?

## **Drug regulation in the US and the UK**

While drug regulation in the UK and the US has a more extensive history, I will not get into this but suffice with drawing out a few comparative points with relevance for the Vioxx case. Some differences to the way that drug regulation developed in the UK and US are of particular relevance to the current regulatory cultures.

Medicine regulation until the 1960s was existent but rather crude and took the form of legislative banning of, for instance, arsenic in the 19<sup>th</sup> Century and making opium and cocaine prescription only drugs in the 1920 UK Dangerous Drugs Act (Abraham and Lewis 2000). In the US, high consumer prices of medicine had resulted in widely publicised congressional hearings and a high profile investigation into drug pricing during the 1950s. This, in time, lead to the 1962 Kefauver-Harris Amendment to the existing drug Bill demanding FDA licensing of drug manufacturers and warnings of adverse effects as well as drug efficiency (Abraham 1995). In Britain the NHS was introduced under the Labour Government in 1948 giving the state a particular concern

with the efficiency and cost of medicines and resulting in an official classification of prescription drugs according to evidence of their therapeutic value. At the same time, a concern for the export value of pharmaceutical products were important for the reluctance with which the government regulated medicines, as for instance expressed by the Ministry of Health's Parliamentary Secretary in 1960: "unwelcome as restrictions were, there was a duty to safeguard the health of the public" (Abraham 1995: 59).

More consistent and coherent drug regulation took its present form in the 1960s following the thalidomide scare where approximately 10.000 children were born with deformities as a result of their mothers taking anti-nauseating medicine while pregnant. In the US, an FDA medical officer had suspected safety concerns with thalidomide and delayed its approval. As a result, the FDA gained a high level of trust in its ability to ensure public health without interference of economic industry interests (Lofstedt 2007). In the UK some 400 mothers had been affected by the thalidomide disaster, however, the British response was more receptive to industry interests than the FDA. This was possibly due to the less high profile that the drug safety issue in general had gained during the 1950s in comparison with the US. Public pressure in Britain started to show itself in favour of a drug regulation reform and resulted in a general public mistrust towards pharmaceutical products.

The Thalidomide disaster made the need for vigorous scientific testing of drugs apparent in order to avoid similar unacceptable side effects from drugs with a large potential for causing harm to its users. This resulted in criticism of the testing procedures and the complete lack of consistency, resulting in drug information to authorities, health care professionals and patients that was industry biased and incomplete. This resulted in both Britain and the US in a system where the drug companies were responsible for conducting the clinical trial testing as a centralised testing authority was deemed "neither desirable nor practicable" (ABPI annual report 1963 quoted in Abraham and Lewis 2000: 51).

The Committee of Safety of Drugs (CSD) in the UK was set up to ensure safe pre-marketing drug approval and evaluate drug safety based on the information supplied by the pharmaceutical companies. It's chairman, Sir Derrick Dunlop, and its members were deemed to be beyond any influence but the scientific considerations (Abraham and Lewis 2000: 51). The principle of independence from industry interests were part of the organisational design from the beginning but failings have often been pointed out, as the

independence of CSD was, largely, assumed and the necessity of working closely with industry and the ABPI (Association of the British Pharmaceutical Industry) was part of the institutional set-up. The overlaps between medical-professional and health-policy networks further enforced the intertwining of industry and public health concerns. Both CSD personnel and health care professionals often had research ties and industrial interests within particular pharmaceutical companies or went on to work for industry. The network form of governance were furthered by the establishment of the industry funded (MCA) Medicines Control Agency in 1989 with a director, Keith Jones, picked from industry and the establishment of 'business units' to promote more informal ties with industry and an aim of reducing drug approval time.

The US legislation had, to some extent, been in place to ensure drug safety prior to the thalidomide scare, although drug efficacy testing was less present. Regulation was thus tightened in 1962 after a process of high profile public debate and heavy industry lobbying of the bill (Abraham 1995). The reform also resulted in a review of some 4000 drugs already approved by the FDA where only 2000 of these were considered effective and 600 were banned. Contrary to the British health authorities, the FDA included scientists with openly adversarial relations to business and in 1974 complaints of industry bias lead to an extensive Congressional investigation of the FDA. In the first instance, FDA conducted its own investigation, which, unsurprisingly, concluded that there was no industry bias or improper conduct within the agency. This was reviewed and resulted in a highly critical report where FDA was accused of 'neutralising' industry critical scientists.

At certain times in both the UK and the US there have been political pressure for minimal regulation, as was the case under Thatcher who actively furthered deregulation in the form of a trial exemption scheme from 1981, where a speedy approval process would rely on data summaries only (Abraham and Lewis 2000: 61).

In the UK, the medicine regulation can, at least partly, be conceptualised in terms of overlapping medical-professional and health-policy networks, which include health care professionals within and outside of the NHS and industry actors who exert some influence on the health and medicine policies and regulations (Salter 2004). The FDA has, traditionally, been in more adversarial relations to industry and has been under more public and Congressional scrutiny within a political climate that was quite critical of the pharmaceutical industry. However, as Abraham (1995: 81) points out, it is easy to

overstate the neutrality of the FDA as the 1970s inquiry into 'neutralisation' polices indicate.

## **Vioxx and the Failings in Medicine Regulation**

Vioxx was launched in 1999 and both the UK and the US the safety review agencies had been aware of the VIGOR study's findings of a 4 times higher likelihood of heart attacks for Vioxx (rofecoxib) compared to naproxen (an NSAID). The agencies had also received a number of adverse effect reports from health care professionals indicating the increased risk (MCA 2000). However, both the FSA and the CSM went along with Merck's explanation that the standard NSAIDs had protective qualities for heart problems (CSM 2000). It was not until the Merck withdrawal in September 2004 that action towards other Cox-2s were taken and safety reviews were reconsidered. This sparked a number of events that indicated that a regulatory failure had taken place.

First of all, the US Senate conducts a hearing into the FDA, Merck and Vioxx where the whistleblower, Dr. Graham, accused FDA officials of threatening him into suppressing his epidemiological findings that indicated a safety concern with Vioxx (Graham 2004). In April 2005, FDA tells Pfizer to voluntarily withdraw the Cox-2 inhibitor Bextra and in May 2005, Merck's CEO, Raymond Gilmartin, resigns followed in September by Lester Crawford from the FDA. Within Europe, the safety concerns with Cox-2 resulted in a 2005 EMEA (European Agency for the Evaluation of Medical Products) safety review and in the UK the pharmaceutical sector came under critical scrutiny in the House of Commons Health Committee's inquiry into *The Influence of the Pharmaceutical Industry* in 2004-2005 which was highly critical of the industry influence into the MHRA review process. In the light of the new risk assessment, it was not just the safety that were under critique in both a UK and a US context, also the over promotion and prescription of Vioxx was pointed out indicating the commercialisation of public health products and medicines (House of Commons Health Committee 2005: 96).

For several critical voices in the debate over Cox-2, the background for the regulatory failure can be sought in the extent to which the regulating agencies have been guided by industry interests and economic concerns rather than a concern for patient safety (eg. Avorn 2004; Angell 2004). This assumes that each stakeholder has particular interests invested in a risk decision-making process and that a tension exists between the core actors in the medicine regulation process so that a political triangle of state (or welfare

state) citizenship and medicine emerges (Salter 2004). Abraham (1995) explores this dimension in relation to regulation of the pharmaceutical industry. It here seems to be a logical starting point in the study of competing interests in health care policy and drug regulation to dismiss a classical pluralist model of the state where the political system consists or the sum of the aggregated interests in society and the decision-making process, in principle, is open to diverse influences according the relative strength of existing interest organisations (Dunleavy and O'Leary 1987: 35). The concern is that some grievances and interests can remain more or less excluded from the political system emphasising the inequality in access to the political and regulatory system. Abraham points out that with time a bias towards industry interests can develop within the regulating authorities and commissions thus drawing on a more elitist notion of state and stakeholder interaction (Abraham 1995: 23).

Partly following this argument but drawing different conclusions, Lofstedt (2007) argues the regulatory crisis is linked to an erosion of trust in the pharmaceutical industry as well as the agency responsible for its regulation as a direct result of the Cox-2 scandal. This loss of trust in the sector's ability to regulate secure public safety has had two major consequences. In the first instance, it has lead to an FDA policy of dissociation from industry in order for an Agency that has traditionally enjoyed high levels of trust, to counter the criticism of being 'too cosy' with industry. Moreover, the loss of trust in the regulating authority following high profile risk events has, historically, led to tougher regulation and, likewise, the recent drug recall cases, e.g. Rezulin, Vioxx, Bextra, have prompted tightening in the drugs control. It has even resulted in a 'crisis of identity' where the Agency looks towards reform in order to regain public trust and reassure the public that drug safety can be provided.

It is sometimes pointed out that the pharmaceutical industry is responsible for testing its own products, in which they have large investments, thus, questioning the impartiality of the scientific results obtained (House of Commons Health Committee 2005). For the drug industry this remains uncontroversial, as pointed out by a senior scientist in GlaxoSmithKline(GSK):

I have no doubt that the first duty of any research and development organization is to look for, find and develop new medicines which are capable of making substantial contributions to the profit and turnover of our companies.... This, however, need not worry any of you because the only way of achieving our objective is to find better medicines for coming illnesses (Jack 1979)

However, the Vioxx case shows that this could be a problematic claim in the light of the contestability of the trial results supplied to the public authorities. These result are, indeed, given meaning through the challenge of disagreeing scientists claiming that the scientific enquiries conducted by Merck were either flawed or, at least, insufficient. The question of funding was, therefore, important in the pointing out of the regulatory failings. There are still no calls for a centralised and independent system of drug testing but the House of Commons Health Committee recommended specifically that the MHRA more routinely conducts audits of the raw data rather than the summaries of the trials conducted by the drug makers (House of Commons Health Committee 2005: 104).

The Vioxx case resulted in a thorough re-examination of the inadequacies of the regulatory system. These have, in particular, been linked to an industry bias in drug regulation and a failure to ensure the public health. As the history of drug regulation has shown, this is no new consideration when regulation is critically examined. It raises a number of theoretical questions of how this dualism between private economic interests and general public interests can be understood. Some new developments within policy theory can be considered, namely insights in relation to deliberative policy-making and more discursive conceptualisations of 'interests'. If ideal regulation is a matter of ensuring 'public health', how can this be conceptualised?

### **Some Theoretical Perspectives: The Contours of a Reform**

Several issues emerge from these considerations of regulatory failure. The overriding concern seems to be one of inclusion and exclusion of different interests in the regulating process. When regulating medicines in order to ensure their safety it is, of course, neither possible nor advisable to exclude pharmaceutical companies from the process. However, an industry bias seems to be highly problematic and can result in risk to public health due to commercial concerns taking precedence over safety, for instance when highly profitable drugs are marketed either directly to consumers (US) or to health care professionals. As Fairman points out, two strategies can be adopted to avoid an industry bias, either one of openness and transparency, or to include more diverging interests into the policy process (Fairman 1999: 103). As openness does not in itself secure against an industry bias, the policy literature tends to look towards more deliberative and democratic practices in risk regulation to ensure public health.

One of the forms that inclusion takes in the debate over governance is through the suggestion of ‘partnerships’ in the pharmaceutical area. Both industry representatives and health authorities seem to lean towards this term that dovetails nicely with new theories of governance through networks and certain versions of deliberative democracy. A senior executive from Pfizer expresses his approach to the relationship between industry and the regulators:

What we need are critical partnerships. And by that I mean we need to sit down with the regulators and develop a system, and academia etc. and scientists, and develop a system which we can all support and has this wonderful integrity and actually does what it intends to do. In the case of pharmaco-vigilance, identifying safety signals and integrate them with the benefit statements as well (industry interview 16/3 2006).

From an industry perspective, partnerships do not necessarily mean patient or consumer inclusion, but the inclusion of regulators, industry and independent scientists, thus replicating to some extent the problem that occurred already in the establishment of the regulatory system after the thalidomide disaster. The existing system relied on scientific representation to be neutral and free from industry bias. While Dr. Graham’s role in the Vioxx case show that independent scientists have a very important role to play in pointing out systemic failures and biases, it does not in itself secure a democratic element in the process of drug safety regulation.

Advisory committees are a privileged and even indispensable element for policy advice in technical decisions due to the high level of knowledgeable expert consultants and relatively low cost (Jasanoff 1990: 1). Moreover, independent expert involvement brings legitimacy to the process in relation to the public: “deliberately because they are independent, they are not tarnished by [the] political shenanigans of government” (G. Hollis cit. in Phillips et al 2000, vol. 15: 36). Jasanoff points out that in British decision-making with its use of advisory committees, trust depends on the individual merits (professional, scientific and personal) of the committee members rather than legalistic and democratic procedures (Jasanoff 1997: 228). It thus contains the characteristics of a technocratic regulatory system where a knowledgeable elite is considered the best exponent for the general public interest rather than a (more pluralist) system build on competing private interests. Irwin’s distinction between two main policy models, the ‘expert’ and the ‘democratic’ or ‘representative’ model, in dealing with environmental threats could be relevant for the regulatory shift in managing drug risk, although the

democratic potential always will be limited due to the highly scientific nature of the drug approval process (Irwin 1995: 64-65).

The regulatory change relies on a discursive articulation of democracy as being able to deliver policy outcomes that are in the general public interest – just as it was the case with the legitimacy of the technocratic meritocracy. This change follows a more general trend in policy-making away from pure representation towards a participatory and multi-layered style of governance where policy-networks and several international, regional and national levels provides input into the system. During this complex process stakeholders, the public, experts and politicians on several levels contribute to a framework that produces public purpose within drug safety.<sup>1</sup> However, for Salter the fundamental basis for power in the medical sector continues to be based on trust despite the rise of patient organisations and more democratic forms of governance within the NHS and elsewhere, thus leading to the idea of the ‘illusion’ of patient power (Salter 2004).

## **Conclusion**

In a tentative conclusion, the Vioxx case can be understood as a disrupting force for the existing regulating regime. The scandal following the FDA whistleblower, media generated public debate and parliamentary inquiries into pharmaceutical policy made the failings within the existing system visible and put renewed focus on how to ensure public safety in the area of medicine. For many commentators on risk policy and regulation reform means ensuring that a deliberative or democratic element is included in the regulatory reform. In the area of drug safety this is particularly challenging due to the highly scientific and specialised nature of the drug trial system and the risk assessments. It does not seem like a doable alternative to remove the industry responsibility of conducting randomised clinical trials and centralise it within the state. The scientific committee system is therefore necessary to ensure audit of the trial results. While more resources and personnel may ensure a better audit, the challenge lies in including patients’ and the public’s interests. It has partly previously been assumed that a thorough

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<sup>1</sup> This move has been described by Marcussen and Torfing who define network governance in accordance with discourse analysis as: “...a horizontal articulation of independent, but operationally autonomous actors; who interact through negotiations; transpiring within a regulative, normative, cognitive and imaginary framework; that to a certain extent is self-regulating; and which contribute to the production of public purpose within a particular area (Marcussen and Torfing, 2003: 7).

and independent scientific process is sufficiently to obtain this goal, however, the Vioxx case shows that more diverging interests could be at stake and require some form of inclusion.

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