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The story of Vioxx—no pain and a lot of gain: ethical concerns regarding conduct of the pharmaceutical industry

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The story of Vioxx (rofecoxib; Merck Sharpe & Dohme, Whitehouse, NJ, USA)

The history of the development of nonsteroidal anti-inflammatory drugs (NSAIDS) is a combination of great pride and great shame. Great pride in the application of bench pharmacology (the discovery of selective cyclooxygenase 2 [COX-2] inhibitors) into clinical practice and great pride in the stunning commercial success of these "blockbuster drugs",[a] but great shame with the abrupt withdrawal of a drug considered to be the "holy grail" for pain relief.[b] How could this have happened, or, more importantly, what are the lessons we can learn from the story of Vioxx?

For over 40 years, starting with aspirin, NSAIDS have been used for pain relief in inflammatory diseases. As new molecules appeared on the market the indications for their use broadened to almost any painful (inflammatory or not) condition. But, just like steroids, their use was limited by toxicity, notably gastrointestinal bleeding and renal insufficiency [1]. It was the discovery of two isoforms of COX (COX-1 and COX-2) in the early 1990s that ignited interest in developing the class of COX-2 inhibitors, of which Vioxx is a member. The plausible mechanism of action offered was that selective COX-2 inhibition results in pain relief, while *sparing* the gastrointestinal side effects seen with the use of non-selective traditional NSAIDS.

This one-sided emphasis on lack of gastrointestinal toxicity, while largely ignoring other adverse events, was, in fact, the motto behind the marketing of the first selective COX-2 inhibitor, celecoxib, better known as Celebrex (Pfizer, NY, NY, USA). Its promotion was based on a trial named CLASS [2] (Celecoxib Long-term Arthritis Safety Study), focusing on its safety profile, yet at the same time underscoring the fact that it was at best a very weak COX-2 inhibitor and at worst no better than the traditional, but much cheaper NSAIDS [3].[c] At the same time, another agent, rofecoxib (Vioxx) a more robust molecule, was trialed. Its superior COX-2 selectivity, combined with its excellent gastrointestinal safety profile, as shown in the VIGOR (Vioxx Gastrointestinal Outcomes Research) study, were extremely encouraging [4].

So, with these data in 1999, and well before the publication of the VIGOR study results in the *New England Journal of Medicine* in November 2000, Vioxx was approved for widespread use by the United States Food and Drug Administration (FDA), allowing an aggressive and successful marketing campaign.[d] Unfortunately, this is where the story goes sour. What was curiously ignored in the report of the VIGOR study was the fact that Vioxx carried a five-times(!) higher risk for myocardial infarction, which was explained by the authors at the time to be due to a potential cardioprotective effect of the comparator drug used in the study; namely, naproxen [5]. This farfetched pleonasm, which

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[a] Worldwide annual sales of NSAIDS are estimated to be around 20 billion US dollars
[b] See: Merck announces voluntary worldwide withdrawal of Vioxx. News release. Whitehouse Station, NJ: Merck 2004. www.vioxx.com/vioxx/documents/english/vioxx_press_release.pdf
[c] The editor of *JAMA* at the time, when he found out that Celebrex was not as good as presented, was interviewed in the *Washington Post* saying: ". . . I am furious . . . I look like a fool . . . we are functioning on a level of trust and that was perhaps, broken . . .". Susan Oakie, *Washington Post*, August 5, 2001, A11
[d] In those 18 months, Merck Sharpe & Dohme and Pfizer grossed more than 3 billion US dollars

was not based on any clinical or theoretical evidence whatsoever, apparently satisfied the FDA at the time, but was quickly rebutted by many authors once the VIGOR study results where published.[e] Despite all this, it was only in April 2002 (or around 4 billion US dollars later), that the manufacturers were instructed by the FDA to include certain precautions about the cardiovascular risks of Vioxx in its package insert [6]. Why such delay occurred remains unclear.

Despite the attempts of the manufacturers to reconfirm the favorable cardiovascular safety of Vioxx with "education" symposiums and "expert panels", the metaanalysis of data showed unequivocally that Vioxx carried a significantly increased risk for myocardial infarction, thrombo-embolic events, hypertension, and heart failure. Probably the study that finally tipped the balance and compelled Merck to withdraw Vioxx was the APPROVe (Adenomatous Polyp Prevention On Vioxx) study [7]. This unpublished trial, which was planned to show the virtues of selective COX-2 inhibition on tumor transformation of polyps (COX-2 is thought to play a role in carcinogenesis), proved again the only previously known fact—that with Vioxx you have a higher risk of having a heart attack [8].

How could this have happened?

Unfortunately, Vioxx is not the first drug to be withdrawn from the market, nor is Merck the first drug company to have to do so. Knowledge evolves and theory might be proved to be false; thus, the fact that what was thought to be a beneficial effect of COX-2 inhibition (less gastrointestinal bleeding) turned out to be an adverse effect (more cardiovascular events)[f] is not troubling as such. What makes the Vioxx story disturbing is the fact that none of the three major forces in this 5½-year affair—the FDA, the National Institute of Health (NIH) and Merck—fulfilled their responsibility to the public. How could this have happened?

In order to answer this question it is important to analyze the roots of the omnipresence and omnipotence of the pharmaceutical industry in our modern lives, an industry that has tripled its size between 1980 and 2000 and has been consistently ranked as one of the top three most profitable industries in the world with an estimated gross domestic product of 200 billion US dollars.[g] In the United States, one of the landmarks in this development is the Bayh-Dole Act (also known as the Technology Transfer Act, 1980), which enabled publicly funded research (mostly sponsored by the NIH) to generate patentable inventions. This law was originally intended to serve as a financial incentive for universities and other academic research centers to manage their intellectual property wisely. Yet, in fact, it created a perverse system, where publicly funded research was sold with monopoly rights to private hands, preventing the diffusion of cheaper generic drugs. So here was a system where, for example, a drug called *Expensodyne* is developed with research paid for by tax money; it is sold to a private company, called *Greedy Inc*.; patented for a period of at least 10 years in order to avoid selling the generic form *Cheapodyne*; and during all this time it is sold to patients at exorbitant prices.

But, alas, the plot thickens. All are convinced that *Expensodyne* is needed because it is better, and the reason it is expensive is to ensure the continuing research and development of future new and improved drugs, such as *Expensodyne plus* and *Expensodyne forte*. Unfortunately, neither of these myths is true. Drugs are seldom tested against *other* drugs, but, rather, against placebo, thus only testing their relative and not true efficacy. Furthermore, since 1998, more than three-quarters of the 415 new drugs approved by the FDA were only minor modifications of older molecules, referred to as "me-too" drugs. So *Expensodyne*, thought to be better than the old cheaper drug, is compared to a sugar pill, and is then sold at high prices in order to allow *Greedy Inc*. to develop a more expensive *Expensodyne plus* "me-too" version, and so forth.[h]

For this unfortunate practice to sustain itself, three major conditions must be satisfied. First, "me-too" drugs must accommodate very common lifelong chronic conditions. Second, the market is interested in developing drugs for *paying* customers (so the poor, the sick, and the dying are naturally excluded). Third, the market needs not only to be large but also "elastic", so that new indications for the drug's use can be found, in order to add a continuing influx of patients. What does this sound like? Exactly—Vioxx, the perfect match. An anti-inflammatory drug for a chronic condition (arthritis), meant for paying customers, which can easily be used for *all* (not only inflammatory) types of pain.

Nonetheless, this sort of exploitation was not supposed to happen. The NIH should have required that

[e] Konstam MA (2001) *Circulation*; 104:2280–2288; Ray WA (2002) *Lancet*; 359:118–123; Diepe PA (2004) *BMJ* 329:867–868, to name a few

[f] The plausible mechanism which emerges is that selective COX-2 inhibitors suppress platelet vasodilator prostaglandin prostacyclin (PGI2), without concomitant inhibition of platelet vasoconstrictor prostaglandin thromboxane (TxA2), thus exposing predisposed individuals to a greater risk of myocardial infarction. For further reference, see Fitzgerald GA (2003) *Nature Reviews Drug Discovery* 2:879–890

[g] For a detailed discussion, readers are referred to the excellent book of Marcia Angell (2004) *The truth about drug companies: How they deceive us and what to do about it?* Random House, New York, NY

[h] Idem pp 74–93

public research be left in the public domain, and should have demanded that royalties be returned to them and not exclusively left to private hands. The FDA could have issued compulsory licensure if drugs were not made "available to the public on reasonable terms" (as specifically required by the Bayh-Dole Act).[i] Unfortunately, none of this has been done, causing a malignant ripple effect, where drugs are overpriced, doctors receive 11 billion US dollars worth of "free samples" and are lured into anti-competitive practice, illegally promoting drugs for unapproved uses and engaging in direct-to-consumer advertising, colluding with generic companies to keep cheaper alternatives off the market.[j]

What lessons can we learn?

The Vioxx story reflects poorly on the process that leads to drug approval. In this chronicle there is a combination of aggressive marketing and complacency of drug regulators. The FDA retained a passive position, waiting for more harmful data to accrue despite signals that something was wrong, while allowing Merck to continue vigorously selling their product. The result: not only were patients exposed to a bad outcome but they were also left confused, asking which drugs should we trust?

It is, in fact, the question of trust, mistrust, information, and misinformation which is the central theme of the ethical analysis of this affair. Thus, it is of interest to attempt to delineate any difference of individual moral agency in the medical versus the business milieu. In general, ethical conduct in modern medicine has been heavily influenced by *deontological ethics* (ethics of duty); namely, those of Immanuel Kant. He stated that the self is autonomous only when it imposes upon itself personal rules of conduct that are logically compatible with universal principles of reason (categorical imperatives); therefore, treating others as ultimate recipients of moral agency and not as simple means to self-interested ends.[k] In other words, moral conduct (adhering to categorical imperatives) renders the individual free (autonomous), and this freedom (autonomy) in exchange allows the individual to continue to behave "morally". Thus, *moral principles and daily practice (praxis) are intimately linked* and shape the imminent moral behavior (for example; by refusing to lie and to instrumentalize patients[l]).

On the other hand, in the "ethics of business", the modern capitalistic corporate world bases its moral order on individual liberty by demanding minimal public interference ("the self-made man"), without a categorical need to adhere to moral imperatives. Thus, although fraud and extortion are normatively unacceptable, and equal individuals are expected to negotiate while respecting promises and contracts, these moral principles remain *minimal and negative*.[m] In other words, individual freedom (liberty) *may or may not* depend on moral conduct; hence, *moral principles and daily practice may be divorced from each other*, accepting intolerable conduct (e.g., using misinformation as a strategic tool). This is, of course, in marked distinction from strict medical codes, which are *maximal* and *positive* (e.g., duty of care, ideal of life) and practiced in the spirit of virtuous ethics. This practice, Aristotelian by nature, strives for professional excellence rather than a moral minimum of "not getting in trouble". Thus, the excellent practice of medicine (professionalism) is intimately linked to the moral excellence (virtue) of the physician practicing it.[n]

Thus, inherent differences in the interpretation of moral demands to the free individual exist between the medical and the corporate worlds. Individual moral agents in medicine are *obliged* to adhere to deontological values in daily practice in order to maintain autonomy, while individuals in the corporate world may not *always* require this in order to protect their liberty. So if, indeed, big corporations are unlike medical institutions and businesspeople are unlike doctors, it is not surprising that they do not speak the same ethical language and may not understand the relevance of incorporating moral criteria (such as respect of autonomy, non-maleficence, beneficence, or justice) into day-to-day operation. This "real-world" mentality (versus the "unreal" ideal Kantian or Aristotelian one) with the sole imperative of profit (which is definitely not one of Kant's categorical imperatives), may quickly slip into a mentality of "moral immunity", where *everything* is permitted in the name of financial gain. Thus, although both bioethics and business ethics are new kindred vogues of applied ethics, how can one overcome this gap and merge bioethics with corporate interests?[o]

In our modern biotechnological world, it is possible and absolutely necessary to negotiate tensions between

[i] Idem pp 68–69

[j] Idem pp 115–118. It is also noteworthy that the Hatch-Waxman Act, Drug Price Competition and Patent Term Restoration Act, 1984, actually provided up to 5 years *additional* patent life for brand-named drugs, although originally it was meant to improve market conditions for generic drugs

[k] L'éthique de Kant. In: Métayer Michel (2002) *La philosophie éthique*, 2nd edition, Editions du Ranouveau Pédagogique, Quebec, pp 52–75

[l] It is from this maxim that other ideas, such as respect of autonomy, responsibility, and informed consent have defined the very nature of modern medical practice

[m] Idem, L'éthique des affaires: pp 228–255

[n] See, for detail, Pellegrino ED (2002) *Mount Sinai J Med* 69:378–384

[o] For a more elaborate discussion of this topic, see Rahul K. Dahanda (2002) *Guiding Icarus*. Wiley-Liss, NY

these two worlds, and to avoid the repetition of stories like that of Vioxx.[p] This, however, entails solutions on three separate levels: epistemological, legal, and ethical. In terms of knowledge and correct methodology, the measures to ensure drug safety before definite licensing are relatively straightforward. Drug companies need to register all randomized controlled trials prospectively and allow all data on serious adverse events to be *publicly* accessible. This, in turn, will allow the independent and timely update of systematic reviews of these adverse events. Another possibility is to create an independent institute which oversees the clinical testing of drugs within the NIH, thus ensuring that clinical trials serve a genuine medical need and do not reinforce indirect marketing (i.e., phase IV studies).

By contrast, limiting pharmaceutical omnipotence by legislation is much trickier. Exclusive marketing rights are undesirably long and drug companies have too much control over clinical research, as well as medical education, for their products, thereby sustaining a situation of developing more expensive "me-too" drugs solely for commercial gain. One possibility is to strengthen the FDA as an independent agency by appealing against the Prescription Drug User Fee Act (1997), which authorizes drug companies to pay a "user's fee" to the FDA for every drug reviewed, thereby creating a clear financial firewall between the FDA and the industry.[q]

Finally, what can be done from an ethical point of view? First, it is necessary to recognize that powerful financial incentives can induce tautological circular reasoning (my mind is made up—don't confuse me with facts . . .),[r] using medical research and consequent publications to *obfuscate* rather than provide guidance. Second, it might be of interest that, in cases of conflicting medical data (as with Vioxx), each practitioner tries to apply a "research ethics committee" approach to their daily practice [9]. This "good clinical practice" may seem burdensome when applied to *every* medical act; however, informing patients about potential adverse side effects (which need not be exhaustive) does fall within the scope of duty of care. In the case of Vioxx, there is no doubt that mentioning the increased risk for myocardial infarction would have curbed the unrestricted use of this "me-too" blockbuster drug. This approach does not require a resolution of the medical controversy, but rather, an open and direct approach to patients. Thus the prudent doctor prescribing Vioxx would have added a simple statement: ". . . and in the VIGOR study we found that Vioxx was associated with a five-times increased incidence of heart attack when compared to another anti-inflammatory, naproxen . . ."

In summary, the bottom line of the Vioxx story is that misleading information about the efficacy and safety of a new medicine can cause confusion at all levels of the therapeutic chain and can have serious effects on public health. Attempts to bias clinically relevant information from health professionals, thought to be needed to protect patients from injury, and to protect health services from unnecessary waste, are contrary to public interest and, in the long run, are counterproductive. Corporate involvement *per se* need not compromise moral integrity; however, *bioethical* reflections must be taken into account.

[p] Not all agree that this is possible. Carl Elliot explains his reservations regarding the melding of bioethics and industry by saying: ". . . I worry that each corporate check cashed takes us one step closer to the notion of ethics as a commodity, a series of canned lectures, white papers and consultation services to be purchased by the highest bidder and itemized on an annual budget report . . .". From Elliot C. (2001) "Throwing a bone to the watchdog." *Hastings Center Report* 31:10

[q] This Act will expire in 2007. Reference in footnote g, pp 237–59

[r] In this case, Vioxx was sold as an improved COX-2 inhibitor to compared with Celebrex due to its superior gastric protection (desired effect). When its cardiotoxicity was discovered (adverse effect), Celebrex was then marketed to be better than Vioxx, due to its superior cardioprotection (desired effect), despite its providing no improved gastric protection (undesired effect)!

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