

Safety standards: an urgent need for Evidence-Based Regulation

P. Kourilsky¹ and I. Giri²

¹Collège de France, Collège de France, 11 place Marcelin Berthelot, 75231 Paris Cedex 05, France

²Access conseil, 20 avenue Henri Grellou, 91370 Verrières-le-Buisson, France

Received: 2 July 2008 – Revised: 6 October 2008 – Accepted: 16 October 2008 – Published: 3 November 2008

Abstract. “Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.” (Sackett et al., 1996).

This opinion article describes and analyses some of the consequences of the ever-growing stringency of regulatory standards in the field of drugs and vaccines for human health, with distinct issues in the developed and developing countries. It is argued that the cost and benefit of safety standards, prior and after implementation, are not sufficiently evaluated, nor sufficiently informed by science. We suspect that, as a result, significant amounts of public and private money might be misspent, because assessments of risks/benefits are often questionable, sometimes out of context and inadequate. It is suggested that, just as it happened in medicine 30 years ago, a move towards Evidence-Based Regulation should be promoted. Given the probable and predictable negative impacts on costs and innovation, both in developed and developing countries – particularly in the latter where the needs are huge and the resources highly limited – we contend that such a move is urgently needed.

Keywords. Public health, medicine evaluation, cost of innovation, medicines access in developing countries

Table of Contents

1 Introduction	3.2 The impact of Northern regulatory standards
2 The current situation and the major foreseeable issues in the North	3.2.1 Products from the North have an inadequate cost structure for the South
2.1 The raise in regulatory standards	3.2.2 Regulatory standards provide an efficient protectionist barrier from South to North
2.2 Problems associated with the raise of regulatory standards in the North	3.2.3 Regulatory standards from the North may interfere with making products in the South for the South
2.2.1 Is the risks/benefits balance properly evaluated?	3.3 Single, double or multiple regulatory standards?
2.2.2 Are the increased costs adequate?	3.3.1 The Rotavirus vaccine case
2.2.3 What is the impact on innovation?	3.3.2 The case for multiple standards
2.2.4 Interdependence between developed nations?	3.3.3 The ethical problem
3 The current situation and the major foreseeable issues in the South	4 Discussion
3.1 Neglected diseases	4.1 Regulatory standards and the consequences of their implementation are not sufficiently evaluated
	4.2 The case for Evidence-Based Regulation
	4.3 Why Evidence-Based Regulation is urgently needed



Correspondence to: P. Kourilsky
(philippe.kourilsky@college-de-france.fr)

1 Introduction

Many human activities that have a social impact are regulated. In the production of goods and services, standards and guidelines often frame current and future activities. For example, a new manufacturing plant will be built and operated according to a number of rules that are set in advance. These rules usually, but not always, apply retroactively. They are often devised to cope with new situations, setting a link between regulatory standards and innovation.

An important subset of regulatory standards deals with safety. Safety is a major and growing public concern. The stringency of safety standards has increased continuously during the last decades. In several western countries, the precautionary principle – by which precaution should be exercised, even in the absence of a complete scientific demonstration of the risk – has become a major driver of this phenomenon (Kourilsky and Viney, 1999).

The precautionary principle has given rise to numerous controversies, but has actually penetrated the field of health (Goldstein, 2001; Kriebel and Tickner, 2001; Melton, 2000). Martuzzi (2007) has underlined the consequences of article 174 of the Amsterdam Treaty of the European Union, which stipulates that “Community policy on the environment [...] shall be based on the precautionary principle”: European law, at its highest level, is explicit and uncompromising. As promotion and protection of human health is one of the key motivations of environmental preservation, this provision also involves public health.

Currently, many safety standards are applied to a great variety of objects (cars, toys, etc.) and processes. Safety is one of the regalian rights of any nation. There is a clear link between national regulatory policies, especially safety standards, and international trade. For example, when a nation bans a particular class of toys that do not meet certain standards, it, obviously, also refuses to import such toys from another country.

In this opinion paper, we analyze a number of issues associated with regulatory standards involved in the design and manufacturing of drugs and vaccines for human health. This area is particularly important and sensitive. It has been imprinted by major sanitary crises, such as those involving Hepatitis B, HIV or Creutzfeld-Jacobs contaminations and the “mad cow” episode. In addition, there is a huge gap between the sanitary situation of developed and developing countries where many of the so-called neglected diseases have remained unaddressed. Are current regulatory standards adapted to solve health problems in the North and the South? It will be argued here that, as essential and necessary as they are, some features of regulatory standards may and should be challenged; that there are major questions about their internationalization; and that, by and large, their implementation is not sufficiently based on science.

We concluded that there is an urgent need to develop more scientific activities in the field of regulation. We coin the term

of Evidence-Based Regulation and propose to promote the concept, much in the same way as Evidence-Based Medicine was promoted some thirty years ago (reviewed in Sackett et al., 1996).

2 The current situation and the major foreseeable issues in the North

Most developed countries have created sufficiently autonomous and empowered regulatory bodies to judge and act independently of political and economical pressures. The USA paved the way by creating the Food and Drug Administration (FDA) in 1905. European countries followed individually and the European Agency for the Evaluation of Medicinal Products (EMA)¹ was created in 1995 (Abraham and Lewis, 2001). Most of these regulatory bodies are organized in a similar way, with similar power. They independently fix the standards driving research, development and manufacturing of drugs and vaccines. These standards are usually comparable between countries, otherwise drugs could not be importable from one country to another. For instance, FDA has the right to inspect a manufacturing plant in France and to monitor the quality of the products devoted to the US market. Note that even if a product is manufactured in a given country according to the appropriate standards, it is not usually exportable, unless it has been registered specifically in that country. Registration is a lengthy and expensive process and can last for one, two years or even more, since it includes a thorough verification of all R&D and manufacturing aspects, and often involves additional clinical trials made in the country. Regulatory agencies are powerful enough to close down a manufacturing plant if compliance is defective.

2.1 The raise in regulatory standards

It is not surprising that regulatory standards are rising constantly. As technology improves, requirements increase. For example, a better analytical method improves sensitivity and allows the detection of new impurities. It is to be expected that a regulatory body will request these compounds to be characterized, proven safe, and/or eliminated. Similarly, automates are now judged less prone to error than humans, and regulatory bodies will logically recommend or impose automated manufacturing plants, etc.

In addition, several sanitary crises in the last 50 years – such as Thalidomide in 1962, the infected blood scandal in 1985 and the recent Vioxx case (Bresalier et al., 2005; Kerr et al., 2007) – have aroused a major pressure from the public and the media, such that the public authorities have strived to increase sanitary safety.

The very concept of “risk” has changed, with the spread of the “precautionary principle”. The latter was initially developed as a frame to deal with long-term environmental issues

¹www.emea.europa.eu

(sea pollution, ozone depletion in the atmosphere, etc.) but it became quickly part of the sanitary framework, especially in Europe, and it is gradually entering the law since (Kourilsky and Viney, 1999). The term is less popular in other parts of the world, but the concept of precaution has gained grounds everywhere.

Finally, a number of major law suits have increased even more the sensitivity of safety issues. In several cases, drug companies have been sentenced to pay compensations which are considerable enough to threaten their existence. This trend is facilitated by legal mechanisms such as the class actions in the US. In France, a Prime minister was driven to High Court, and then cleared, in the infected blood case. In general, it may be suspected that drug companies will often fear for their revenues and their image, while public officials in charge may choose to be exceedingly cautious. As independent as they are, regulatory agencies cannot remain insensitive to the weight of public opinion.

All these factors concur to increase the stringency of regulatory standards, which raises a number of questions. We choose here to discuss the four following ones. First, is the risks/benefits balance properly evaluated? Second, are the costs adequate to the social benefits? Third, what is the impact on innovation? And fourth, is the inter-dependency of the national systems in the international network of the North properly managed?

2.2 Problems associated with the raise of regulatory standards in the North

2.2.1 Is the risks/benefits balance properly evaluated?

An optimal risks/benefits balance is supposedly the best trade-off between efficiency of a drug and safety for the patient(s) in a certain context (most often national). The case of preventative vaccines is somewhat distinct from that of drugs since millions of healthy individuals, often children, are to be vaccinated. Several observations suggest that the “risk” factor has increased recently.

From 1975 to 1995, the number of surveys required to obtain an approval from regulatory agencies, has doubled and the number of patients included in clinical trials has tripled. Remarkably, phase III vaccine clinical trials involving more than 50 000 volunteers are not uncommon anymore (Vesikari et al., 2006). The mere volume of documents needed for registration has considerably inflated. 10–15 years ago, the paper documentation needed for the registration of a single vaccine required a small truck to be delivered to the health authorities. Today, it is not longer the case, not because procedures are easier but because files are sent electronically.

A significant fraction of this inflation relates to safety. The exact part may be difficult to assess. For example, increasing the size of vaccine phase III clinical trials does not serve the sole purpose of improving the precision of the efficacy measurement. It also aims to permit a more extensive assessment

of potential adverse effects, which were previously evaluated by pharmacovigilance (sometimes called phase IV) after the launch of the product. Whether too much weight is given to safety is a matter of appreciation. Nevertheless, the Vioxx and other recent cases suggest to us that this question is worth being debated.

Commercialized since 1999, this anti-inflammatory was retrieved by Merck on a public announcement on 28 September 2004. The company took this decision (not requested by the FDA) when a clinical trial on long-term effects of the molecule for colon cancer patients revealed an abnormally high death rate from cardiovascular problems among patients taking the medicine for more than 18 months (Bresalier et al., 2005; Kerr et al., 2007).

As the vice president of the French Market Authorization Committee Pr Bergman stated “*supporters of the precautionary principle inside the company preferred to avoid 3 infarcts, even if it led to 8 digestive bleeding*”. Beyond a really complex assessment of the benefit/risk ratio, one may find paradoxical to retrieve a class of drugs thoroughly evaluated with modern procedures, and leave on the market old medicines for which nobody dared to run such trials.

Was it a good choice in terms of public health? Did Merck consider that the drug was not profitable enough with respect to the risk? We will never know if the priority given to cardiovascular risk was thoughtfully motivated, but the media storm was fruitless. In the end, after 3 days of debates, experts from the FDA recommended the comeback of the product, which was obviously impossible. The controversy was further complicated by statements implying that the clinical files had not been properly delivered by the drug company to the FDA (DeAngelis and Fontanarosa, 2008; Psaty and Kronmal, 2008; Ross et al., 2008).

In our opinion, the Vioxx crisis was largely related to the incomprehension of the public faced to a complex assessment, but also to the obsession of the precautionary principle. The latter brings people to think that any secondary effect should have been prevented (Strom, 2006). Indeed, the expectation of a zero-risk is totally illusory and prejudicial to the pursuit of therapeutic innovation: in medicine, taking no risk means doing nothing. The Institute of Medicine (IOM) was asked by the FDA to analyze the case, and concluded that the Agency should strengthen the US drug safety system further² – a recommendation which faces some practical issues (Wadman, 2007).

2.2.2 Are the increased costs adequate?

The raise of regulatory standards has a cost, both in time and investment.

1. The time factor is often underestimated. More complex and heavy procedures may involve significant delays in

²Editorial (anonymous): Reforms on drug safety, *Nature*, 443, p. 372, 2006.

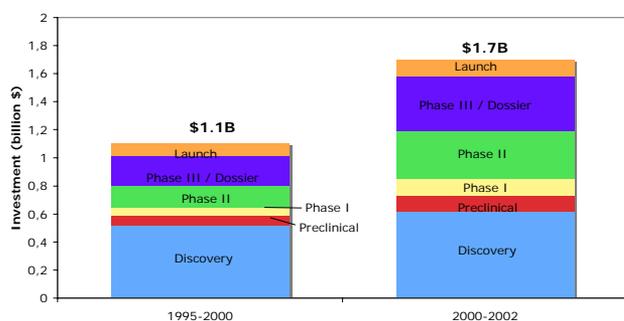


Figure 1. R&D costs for a new chemical entity.

the public release of the drug or the vaccine. In addition, the registration processes which operate nationally and internationally can be quite time-consuming. Some of the induced delays have been alleviated by electronic filing. Regulatory standards can also cause significant delays in R&D. It has to be appreciated that during that time, individuals that might have cured or whose disease could have been prevented may become sick and die. In 2003, an association of cancer patients brought an action against the FDA on this basis (Basu, 2003). More recently, FDA has been challenged for delaying a therapeutic vaccine against prostate cancer (cf. Froese 2008)³.

2. The issue of the financial cost can be raised about R&D. In Industry R&D costs have increased about 3 to 5 folds in 20 years. A recent study used by the FDA in its report "Innovation or stagnation: challenge and opportunity on the critical path to new medical products" evidenced a sharp increase of R&D costs lately, and valued the financial endeavor required to bring a new molecule on the market up to 1.7 billion dollars (Gilbert et al., 2003) (other estimates are discussed below). Indeed, new drugs are more and more expensive. Some of the new anti-cancer drugs reach unprecedented prices, which make them either hardly accessible to anyone, even in the developed countries and/or more and more difficult to be compensated for by social security and health insurance systems.

How much of the increase in R&D cost is due to the raise in regulatory standards?

We could not find data which would allow us to answer this question. We suspect that such data are actually largely missing, implying that the costs and benefits of regulatory standards are not sufficiently evaluated. We are not aware of systematic a priori evaluations of the costs and benefits of a new regulation or a systematic follow-up and evaluation of the established ones, neither by regulatory agencies nor

³Editorial (anonymous): The regulator disapproves, *Nature Biotechnology*, 26, p. 1, 2008.

by other public authorities, or by other academic and private bodies.

No doubt that these evaluations are difficult to perform for a variety of technical, methodological, social and systemic reasons. No doubt as well that they are of importance for regulators, public authorities, consumers and citizens. This is one of the reasons why, as discussed in the end, we plea for Evidence-Based Regulation.

2.2.3 What is the impact on innovation?

Surprisingly, despite the remarkable advances of life sciences, the number of new drugs approved each year has not increased in the last 10-15 years. It looks as if the innovation gap goes wider and wider. May be the easy drugs have been found. May be we need a few better drugs rather than many new ones. Nevertheless, while the development of new medicines has always been a risky venture, it appears that the risk of failure has been skyrocketing lately. According to the same survey from the FDA only 8% of drugs entering Phase I will get to the market. This rate was close to 14% during the previous periods. A variety of reasons, including the very model of R&D project flow within the large companies, may account for the increase (Bains, 2004; Amir-Aslani, 2006). Whether the raise of regulatory standards is, or not, involved is unknown.

Once on the market, a number of drugs fail. Premarketing studies are necessarily limited in time and study participants are often different from "real-life" patients. 51% of drugs are subject to label change because of safety issues discovered after marketing and 3-4% of drugs are withdrawn for safety reasons (Lasser et al., 2002). The costs of post marketing surveillance are significant. Changes and failures impact the R&D expenditures. Some argue that large drug companies could better manage their R&D pipeline (Bains, 2004).

Pharmaceutical companies devote some 15% or more of their total budget to R&D. This figure is unlikely to grow much. At the same time, their financial (market) value relies on their R&D pipeline to a significant extent, with a degree of uncertainty which increases with risks and costs. It is thus likely that the growth of R&D costs is not sustainable for pharmaceutical companies in the long term. We believe that the interest of the patients is to rely on an innovative and stable industry rather than on a fragile and unstable innovating private sector of too high cost.

How much has safety increased over, say, the last two decades, and at which cost? In our view, safety has indeed improved, but was already quite high twenty years ago (as documented by Strom, 2006). But R&D expenses have gone up enormously. Again, if part of the increase is due to safety, the risk benefit balance needs to be assessed. In the worst case scenario, it may be that a significant part of R&D expenses is misspent and even wasted. Actually, the progress in safety and the associated costs could be better documented.

2.2.4 Interdependence between developed nations?

While the national systems converge, they are not identical. Appreciations on safety issues may vary. Moreover, a decision made in one country may significantly affect another. A striking example is the auto-centered assessment of risk on the influenza vaccine in the UK, which could have created a sanitary crisis in the USA.

During summer 2004, the British subsidiary of the Chiron Company informed the authorities that it had a sterility problem on a batch of flu vaccine (Fluvirin). In October, after an inspection from the British MHRA, the production of the vaccine in the Liverpool factory was suspended and exportations were forbidden. This factory supplied less than 20% of the British demand, but almost half of the US one (48 million doses out of the 100 million required). It was already too late for the Americans to contract another factory since all of them were already at full capacity. The decision created a significant shortage of flu vaccine in the USA, where the influenza is a serious disease and causes an average of about 30 000 deaths each year (Thompson et al., 2003).

Rapidly, the CDC reserved the available doses of vaccine (produced by another company) for populations at risk: elderly, newborns and patients suffering from chronic diseases, that is to say 45 million people (Longini and Halloran, 2005). The Department of Health and Human Services (DHHS) tried by all means to find additional doses, even in foreign countries. But other vaccines, for example from Canada, did not have the FDA approval and could not get it before the winter vaccination campaign. In the end, the US authorities managed to get 61 million doses, partly due to the huge efforts of Sanofi-Pasteur (Zambon, 2006).

Julie Gerberding, director of the CDC, announced to the US House of Representatives: *“we are fortunate that the flu season had been relatively moderate so far this year”* ... What is striking is the absence of global assessment of consequences on public health (Glezen, 2006). While this is no excuse for the manufacturing defects of Chiron, nothing was written about a direct contamination of the vaccines lots. The closing of the factory was mostly a decision of precaution. Since the shortage impacted the USA more than the UK, one may wonder whether the authorities felt less concerned by the risk of increased mortality. On the other side, the rigidity of the FDA procedures is disputable: why banning importation of safe vaccines – suitable for Canadians and Europeans – in case of a shortage?

From this experience, the US Department of Health and Human Services learned how to deal with seasonal influenza vaccine and how to redefine the pre-pandemic objectives. Currently licensed vaccines are produced in specialized chicken eggs with a technique that has barely changed in 50 years. The HHS Secretary awards recently more than 1 billion \$ to 5 companies to develop cell-based influenza vaccine, which holds the promise of reliable, flexible and scalable method of producing influenza vaccines

(www.hhs.gov). Two contracts announced in July 2007, will provide funding for renovation and expansion of existing facilities to increase domestic vaccine manufacturing capacity. In July 2007, Sanofi-Pasteur has also doubled its production capacity in the US.

This example illustrates the point that a global assessment of benefits and risks may be important even for a local decision. It also suggests that too much precaution may induce large sanitary risks.

3 The current situation and the major foreseeable issues in the South

Rich countries fare better and better, while health keeps worsening in many developing countries. So far, every year, 13 millions people die from AIDS, Tuberculosis, Malaria, and enteric diseases, while 3 to 5 million deaths caused by infectious diseases could be prevented by the use of existing vaccines, some of which cost only a few cents (Gwatkin et al., 1999). The turn of the millennium was meant by the United Nations to set a milestone towards worldwide wealth and global growth benefiting everyone. The United Nations launched bold projects – the Global Compact, the Millennium Objectives to name a few. The richest countries – at that time gathered in the G7 – acknowledged for the first time at their Summit in Okinawa in 2000 that reducing wealth inequalities between countries should be on their agenda. Growing activism – through initiatives such as “Make Poverty History” or the Porto Alegre Forum – helped prompt a public debate on how the richer bear responsibility to help the poorer⁴.

3.1 Neglected diseases

Along with extreme poverty, the developing countries are also plagued with groundbreaking morbidity levels. Some of it can be blamed on food or water related issues, or wars or political instability. But there is also a long forgotten mass killer: the so-called neglected diseases. Mostly infectious, they account for 90% of worldwide morbidity and at least 1 billion people – one sixth of the world’s population – suffer from one or more of these diseases (WHO World Health Report, 2007). And yet, only 1% of the 1400 new drugs, which have reached the market in the last 25 years, were devoted to these diseases⁵. In the meanwhile, worldwide R&D funding has increased at least 3 or 5 fold, showing that the highly restricted allocation of resources to R&D on neglected diseases originates from a structural problem rather than from the shortage of money per se. Many much needed treatments, vaccines and drugs are either non-existent or inadequate, primarily because there is no international market to drive their development. These diseases are not common in

⁴www.portoalegre2002.org and www.makepovertyhistory.org

⁵www.dndi.org

rich countries and their victims, almost exclusively in developing countries, are too poor to afford the treatments (Mathers and Loncar, 2006). The situation is exacerbated by insufficient healthcare infrastructure, and too often with political instability⁶.

A fundamental issue is the lack of effective demand on the market. From the pharmaceutical companies' side, going on those markets would mean major investments and price reductions, with little chance of return (at least short term). Without incentives, worldwide companies hardly enter those markets. On these issues, industrials have often been systematically demonized. The AIDS crisis has shown how important it is that they adjust their intellectual property management in order to enable local manufacturers to supply those markets. However, their role is not to ensure public health all around the world and multinational companies have to abide by largely deregulated market laws.

The problem is that patients are too poor (Victora et al., 2003) to pay for expensive drugs, which is what pharmaceutical companies do best. In fact, modern treatments and diagnostics can be expensive at three levels: the products, the devices required to use them (electronic instrumentation, etc) and the required staff. These three levels are interactive. Trained medical staff is cheaper in developing countries, but also painfully scarce. Therefore, to be helpful against neglected diseases, a product has to be cheap, and easy to use – ideally simple enough so that non-medical people can be taught to use it with a crash course. Products designed and manufactured in the North do not usually meet these requirements.

Thus, the market is not an adequate determinant of value for neglected diseases: alone, it fails to stimulate the development and supply of these goods, or their adaptation to the circumstances of developing countries. Vaccines, for example, are themselves a “neglected” part of medicines (3% of the worldwide drug market). The existing ones (such as measles) are not sufficiently used in the South, not only because of their cost, but also because of specific implementation problems (needles, cold chain...) and of the weakness of local health systems. As for entirely new vaccines directed against diseases absent in the North, there is not market to drive their development.

To be more specific about R&D, research is largely market independent because many academic institutions, even though they have to comply with their funding bodies, have some freedom to search in areas that have no obvious or short term economic potential. On the contrary, development is largely market dependent. And development costs are usually far superior to research costs and out of reach for most academic institutions, as one will realize by comparing the figure of about 1 billion per new chemical entity to the yearly budget of most research institutes, which is often much lower. Therefore, research is neglected to some extent,

⁶www.dndi.org

but the critical point is development: research on neglected diseases, even if successful, will not, in general, be developed.

As a consequence, when patients are poor, there is no mechanism to finance the R&D that could bring about new medicines for the neglected diseases. Fortunately, a recent burst of philanthropic donations – illustrated by the Gates foundation and others – as well as new international types of partnerships have significantly improved the situation, but have not yet solved the overall problem. The question addressed below is that of the adequacy of Northern regulations to drug and vaccine development in the South.

3.2 The impact of Northern regulatory standards

3.2.1 Products from the North have an inadequate cost structure for the South

The price of the products incorporates the increasing impact that regulation is likely to have on development costs, and manufacturing is largely done in rich regions. Drug development is the costliest step to create a new drug. Setting-up wide-scale clinical trials is very complicated in developing countries. The legal framework that regulates drug environment and trials is clearly universal, but its practical application finds no equivalent in those deprived regions. Merely replicating American and European rules is obviously problematic as they are not meant to fit with situations encountered in the South.

Thus, the cost structure of medicines – even for neglected diseases prevalent only in the South – is so far mostly modeled by the North. Some emerging countries manage to cope with the situation but developing countries suffer from this inadequate cost structure when paying for health products coming from the North.

3.2.2 Regulatory standards provide an efficient protectionist barrier from South to North

The cost and sophistication of the manufacturing of medicines, in part due to the regulatory standards, is such that developing countries cannot, at this stage, make products and export them to the North. This is also a matter of dynamics. Regulatory standards change, and developing countries cannot afford to follow that race, or to match the investments needed to register in the developed countries. Thus, drugs sold in the North are so far solely made in the North, and regulatory standards can act as a protectionist barrier.

3.2.3 Regulatory standards from the North may interfere with making products in the South for the South

One of the most complicated and possibly perverse consequences of the internationalization of Northern standards is

that poor countries that fail to meet them, refrain from manufacturing for themselves, even if they are not formally forbidden to. Thus, even when the local risks/benefit balance is favorable, the local authorities, sometimes under the pressure of international organizations, many choose to endorse Northern standards. Understandably, how could health decision makers accept vaccines or drugs to be distributed in their own countries while considered too risky for people from the rich countries?

This question relates to the hotly debated issue of the “double standard” that needs to be approached and discussed carefully.

There are two major arguments to promote the internationalization of unique regulatory standards. The first is that the best standards should be used by everyone such that everyone benefits from the best products and healthcare conditions. Reciprocally, it is judged unethical that poor people would access health products of a lower quality than those available to the rich. The second argument is economic in nature and relates to trade and free circulation of goods. Poverty is so acute in certain countries of the South that, as mentioned above, these issues may seem somewhat farfetched. However, the situation in emerging countries such as Brazil, China, Cuba and India deserves being further analyzed, because drug industries close to meet, or meeting, the Northern regulatory standards are growing there. Whether drugs manufactured by Brazilian or Chinese companies will freely flow on the American and European market remains to be seen.

Dealing with the ethical issue, two major questions come to mind: who decides what is best for the others? And the second one is: on which criteria?

3.3 Single, double or multiple regulatory standards?

3.3.1 The Rotavirus vaccine case

Rotavirus diarrheas affect around 130 million children every year. Despite a treatment based on oral rehydration, these diseases are a major cause of infant mortality in developing countries, causing around 500 000–800 000 deaths each year (Miller and Mc Cann, 2000; Simonsen et al., 2001), killing one child in 40 during the first 5 years of life (Melton, 2000). In the US, rotaviruses are responsible of more than 3 million diarrheas each winter with 500,000 consultations and from 55 000 to 100 000 hospitalizations. However, and fortunately, only 20 to 100 patients die each year (Tucker et al., 1998). Rotaviruses are responsible of half of gastrointestinal diseases, and the improvement of hygiene is not sufficient to eradicate these epidemics, making vaccination desirable even in rich countries.

An efficient vaccine was first commercialized in August 1998 by Wyeth laboratories (Joensuu et al., 1997). The Advisory Committee on Immunization Practices (ACIP) recommended that every child be vaccinated with 3 injections at the age of 2, 4 and 6 months (CDC, 1999). A survey from the

Center for Disease Control (CDC) had shown that rotavirus infections costed over 1 billion dollars to the US administration each year. The vaccination campaign was judged cost effective.

This vaccine was a commercial success with 1.5 million doses administered the first year (Melton, 2000). However, after a few months of vaccination, the CDC noticed an increase in the number of intestinal invaginations (or intussusceptions) (CDC, 1999b). A small number of patients suffered from this severe secondary effect. An article from experts of the National Immunization Program and the CDC estimated that “assuming a full implementation of a national program of vaccination, 1 case of intussusception attributable to the vaccine would occur for every 4670 to 9474 infants vaccinated”. In October 1999, the ACIP retrieved its recommendation (CDC, 1999c) and commercialization of the vaccine was stopped.

This vaccine no longer had a future in the USA. But as a consequence, the development of this product in countries where it was needed most was suspended. In Africa, Asia and South America, rotaviruses kill 2000 children each day. Clearly their risk assessment is totally different: for some populations, the benefit of being vaccinated largely overpasses the risk of a severe but rare intestinal invagination (Melton, 2000). And yet, how could they accept a product that was not good enough for the Americans? But is it ethical not to use a vaccine that could save millions of lives in developing countries? Those questions were raised at a WHO conference in 2000, where the representation of most deprived countries was symbolic (only Tunisia and South Africa were representing the whole African continent). During this conference (WHO, 2000), the CDC representative clearly stated that the ACIP recommendation was for the USA only, and argued in favor of an early vaccination in developing countries. What is more, epidemiological studies had proven that intestinal invaginations are less prevalent in poor countries. However, WHO concluded to wait for a new vaccine, in spite of the fact that a new product developed by different pharmaceutical companies and tested both in developing and developed countries, could not be expected before 5 to 7 years. It has been noted by a physician-ethicist (Wejner, 2000): “some have falsely assumed that inaction is a morally neutral state. But if one is culpable of vaccine related deaths, then one is also culpable for deaths caused by withholding the vaccine”.

The sad and ironical part of this story is that further studies proved that the withdrawal in the US was not justified, because the risk of intestinal invagination was smaller than suggested by the initial studies (Murphy et al., 2001; Murphy et al., 2003). The NIH even proved that the hospitalization rate for invaginations had decreased in the long run in states where the vaccination had been widespread (Kramarz et al., 2001 and Simonsen et al., 2001). In fact the vaccine triggered earlier an intussusception on patients that would have had this problem eventually. In the end, the benefit/risk balance was still positive (Glass, 2004). But it was

impossible for the US authorities to step back since it could have aroused a wave of mistrust around vaccination in general. And, even if the decision of withdrawal was too fast, it was a rational process in the context of the US, because rotavirus diarrheas are a benign and curable disease there. The problem is that this decision was taken in order to avoid a political risk and media incomprehension, but it was not fully scientifically based and motivated. In addition, the local authorities did not assess the damage that this withdrawal could cause on worldwide sanitary conditions. Arguably, this may have been out of their scope, but it was in the mandate of WHO to check and exploit constructively the situation.

We have stated previously and elsewhere that the precautionary principle may be counterproductive when used hastily, and that it may even go against prevention. The rotavirus case can be interpreted to mean that the rare complications provoked by a vaccine in rich countries were given, even by WHO, more importance than many lives to be saved in poor countries.

3.3.2 The case for multiple standards

With the above example, we cannot escape the question of whether we, in the North, are, consciously or not, exporting our vision and our standards to the South in a somewhat imperialistic fashion. After all, nations have the right to decide for themselves. The argument that many developing countries do not have appropriately trained staff to properly analyze the local situation and make educated decisions is less and less valid. Assuming it is, one could then argue that the highest priority – and somehow the role of WHO – would be to train people to help making the decisions, rather than making decisions in their place.

The other major issue deals with the criteria used to set the regulatory standards themselves. If their goal is indeed to define the proper risks and benefits balance for the local population, two factors come to light. One is factual: risks are obviously not the same nor of the same magnitude everywhere. The other is cultural: the perception of risk through secondary effects is largely dependent on the sanitary, social and cultural context of the region. For example, they are less accepted for new drugs, or for preventive care. Of course, in the poorest countries, where life expectancy often does not exceed 40 years, the perception of risks is completely different. Thus, there is a strong logic basis to favor “multiple” standards, each adapted to a defined context.

3.3.3 The ethical problem

Regulatory standards are designed to protect the safety of people, and are thus closely intertwined with ethical issues. Supporters of the universality of ethics oppose those in favor of ethics adapted to local situations (contextual ethics). The former mix up ethical standards with regulatory standards, and accuse the latter of “double standards”. We agree

that reaching the same standards for every one is probably ideal, but the problem is that this ideal, which every single country – either rich or poor – should tend towards, is being currently implemented at the poor’s’ expenses. While developing countries cannot accept medicines that were not good enough for rich patients (it would mean that their lives worth less because they are poor), rich countries, when establishing their standards, should then take into account their impact on millions of lives in remote areas.

Another problem is that the seemingly obvious statement that “safer is better”, which superficially can be taken as an implicitly ethical principle, is not as obvious as it looks. Actually, the rotavirus example shows that it is not necessarily ethical when faced with its practical consequences (Kourilsky, 2004).

In the end, the resolution of the sterile and dangerous battle between the proponents of universal and contextual ethics might rely on the definition of what is unethical rather than on the opposite. It is clearly unacceptable to provide poor people with drugs and vaccines of insufficient quality. But is it unethical, if so they wish, to provide them with medicines which were extensively used in the North, 20 or 30 years ago, with huge benefits for public health, and few, if any, adverse effects, and are, nevertheless, outdated in the North, because the regulatory standards have changed? We are again at the heart of the matter. How is the validity of the regulatory standards assessed? How are risk/benefit ratios evaluated? And who decides?

4 Discussion

4.1 Regulatory standards and the consequences of their implementation are not sufficiently evaluated

Regulatory standards are indeed essential, inescapable and enormously useful, especially in the field of human health where safety is a major and legitimate concern. This does not imply that they should be immune to evaluation. The actual benefits produced by those regulations have to be assessed, and compared to the costs they may induce before and after their implementation. Certain standards might be reconsidered in view of individual and collective benefits, and at the light of what really happens on the field.

Regulatory standards are constantly raised, while their cost and impact are not systematically evaluated. In our view, it is highly significant that we could not find much solid data on the rational implementation and evaluation of regulatory standards. This situation has major consequences:

1. It leads to suspect that some regulatory standards may simply be useless. If such is the case, the associated costs are unjustified. This is hardly acceptable, especially when dealing with medicines devoted to the poor countries.

2. It makes it difficult to properly assess the risks/benefits balances, in situations where they are the basis of major public health decisions.
3. It favors globalized views and, sometimes, theoretical or ideologically biased ones, by lack of analytical capacity.

In the absence of more data, we cannot estimate the magnitude of the extra-costs which might be induced by undue regulatory standards. Given the huge increase in R&D costs in the North, we suspect that they may be high. We are thus led to raise the provocative question of whether significant amounts of moneys are spent in processes of unproven usefulness. In the North, the consumers finally endorse the extra-costs, but social protection systems getting close to asphyxia, and this issue deserves being carefully analyzed. In the South, much of the health improvements are supported by charitable funds in severely limited amounts. It is somewhat shocking to suspect that part of this money is wasted or misused.

4.2 The case for Evidence-Based Regulation

From the above, we conclude that the regulatory field, at least in the area of human health, which we looked at, is not instructed enough by science. We contend that a situation in which decisions are not sufficiently based upon facts and measures, nor followed up by an objective evaluation, involves a non-scientific attitude.

A parallel can be drawn with medicine. In 1992, the term of Evidence-Based Medicine was coined to promote a more rational practice of medicine that had been advocated since the 70's, in particular by Cochrane (Sackett et al., 1996). In simple words, this move intended to render medicine more scientific and less empirical. Like medical doctors, regulators constitute a powerful community of experts who hold and develop a specific body of knowledge. We suggest that Evidence-Based Regulation should be promoted with the same goals and spirit, as it was done in medicine previously.

It should be mentioned that the putative perimeter of Evidence-Based Regulation is larger than that of the regulatory field per se, and that it represents, in our view, a new area for scientific research. A first point is that, just as science does not belong to the scientists, regulations do not belong to the regulators. More precisely, Evidence-Based Regulation implies the gathering and analysis of data which do not all pertain to the regulatory field. For example, the estimation of the cost of development of a new drug involves significant methodological questions, which go much beyond questionnaires sent out to companies, and rely on an analysis of the R&D pathways in the latter (DiMasi et al., 2003; Bains, 2004). Such estimates are needed to further dissect the cost structure of new drugs and evaluate the induced cost of regulations. Many other issues deserve being documented for the purpose of evaluating risk benefit balances not only prior to, but also after implementation of decisions. Some,

especially those dealing with the state of public health in the developed countries, already are. Others, often in economics, are not. This is especially true if one adopts a more holistic attitude, taking in account the more global aspects of local decisions, in developed as well as developing countries.

Another aspect of Evidence-Based Regulation implies that the community of regulators might make use of a number of rules and procedures which have proven extremely useful in scientific communities. They include peer-reviewed opened communication systems which are currently somewhat lacking in the regulatory field. The rationale is similar to the one which sustains the FACTS initiative⁷. Finally, inherent to Evaluation Based Regulation is the notion of including academic research. This is important in many respects, especially since this research activity must be independent by nature. In particular, information gathered from industry must be validated. The process may face confidentiality issues. However, industry should not be, directly or indirectly in the position of self-evaluation.

We emphasize that promoting Evidence-Based Regulation involves neither an attack upon regulators, nor a defense of industry (or vice-versa), nor a incitement to decrease safety. The overall goal behind the proposal is to have the field better informed by science and, indeed, to make it more rigorous, while possibly to achieve better public protection with less money. The rise in costs might soon be unbearable. New methodologies for clinic assessment, new ways to monitor drug safety (Strom, 2006), and a new vision of preventive medicine probably need to be designed and implemented.

4.3 Why Evidence-Based Regulation is urgently needed?

In prospective, the need is obvious and action is urgent. In the North, the health expenses are climbing up, and will become less and less affordable. In the South, every cent should be optimally used to make progress, either in the distribution of existing drugs and vaccines, or in the development of medicine to control neglected diseases. In this respect, R&D figures provide an illuminating example. If we take the usual (though questionable) figure of 1 billion Euros to develop a new drug, it is hardly conceivable to solve the issue of neglected diseases. Any factor that diminishes this cost is a step forward resolution.

We re-emphasize that challenging regulatory standards, as we do here, does not imply in any way that scientific rigor is relaxed. It is exactly the opposite. The fundamental question is to do at least as well with less money. In this respect, it may well be that the on-going efforts to solve the issue of neglected diseases, with quite limited resources, will actually help the North devising more appropriate rules for the management of health.

⁷Field Actions Science (FACTS) initiative: <http://www.institut.veolia.org/fr/facts-initiative.aspx>

Finally, we consider that the ethical thinking would benefit from being backed up by more data and that Evidence-Based Regulation will help promoting more sophisticated and sometimes better adapted ethical views. Hopefully, it might also help developing the much needed solidarity which sometimes seems to dwindle as wealth increases.

Conflict of interest

The authors declare no conflict of interest related to their ongoing activities, but acknowledge the fact that some of their previous activities may have influenced their views.

Acknowledgement. Thanks to Marine Desbans for her help in analyzing information and writing this manuscript.

Edited by: G. Mainguy

Reviewed by: two anonymous referees

References

- Abraham, J. and Lewis, G.: *Regulating Medicines in Europe: Competition, Expertise and Public Health*, Routledge, London & New York, 2001.
- American Academy of Pediatrics: Prevention of rotavirus disease: guidelines for use of rotavirus vaccine, *Pediatrics*, 102, 1483–1491, 1998.
- Amir-Aslani, A. and Negassi, S.: Is technology integration the solution to biotechnology's low research and development productivity?, *Technovation*, 26, 573–582, 2006.
- Bains, W.: Failure Rates in Drug Discovery and Development – Will We Ever Get Any Better?, *Drug Discovery World*, 5, 4, 9–19, 2004.
- Basu, P.: Cancer patients sue for access to experimental drugs, *Nature Med*, 9, 10, p. 1231, 2003.
- Bresalier, R. S., Sandler, R. S., and Quan, H.: Approve trial investigators: Cardiovascular events associated with rofecoxib in a 3-year randomized colorectal adenoma chemoprevention trial, *N. Engl. J. Med.*, 352(11), 1092–1102, 2005.
- Centers for Disease Control and Prevention: Rotavirus vaccine for the prevention of rotavirus gastroenteritis among children – recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR Recomm. Rep.*, 48, 1–20, 1999.
- Center for Disease Control and Prevention: “Measles, Mumps, and Rubella – Vaccine Use and strategies for elimination of Measles, Rubella, and Congenital Rubella Syndrome and Control of Mumps: recommendations of The Advisory Committee on Immunization Practices (ACIP)”, *MMWR Recomm. Rep.*, 47, 1–57, 1998.
- Centers for Disease Control and Prevention: Intussusception among recipients of rotavirus vaccine, United States, 1998–1999, *MMWR Morb. Mortal Wkly. Rep.*, 48, 577–581, 1999b.
- Centers for Disease Control and Prevention: Withdrawal of rotavirus vaccine recommendation, *MMWR Morb. Mortal Wkly. Rep.*, 48, p. 1007, 1999c.
- DeAngelis, C. D. and Fontanarosa, P. B.: Impugning the integrity of medical science: the adverse effects of industry influence, *JAMA*, 16, 299(15), 1833–1835, 2008.
- DiMasi, J. A., Hansen, R. W., and Grabowski, H. G.: The price of innovation: new estimates of drug development costs, *J. Health Econ.*, 22, 2, 151–185, 2003.
- Froese, P.: Fallout from flip-flops, *Nat. Biotechnol.*, 26(6), 614–615, 2008.
- Gilbert, J., Henske, P., and Singh, A.: Rebuilding Big Pharma's Business Model, in: *Vivo, the Business & Medicine Report*, Windhover Information, 21, 10, 2003.
- Glass, R. I., Bresee, J. S., Parashar, U. D., Jiang, B., and Gentsch, J.: The future of rotavirus vaccines: a major setback leads to new opportunities, *The Lancet*, 363, 1547–1550, 2004.
- Glezen, P.: A Warning Shot: Influenza and the 2004 Flu Vaccine Shortage *JAMA*, 295, 1316–1317, 2006.
- Goldstein, B: The Precautionary Principle Also Applies to Public Health Actions, *Am. J. Public Health*, 91, 9, 1358–1361, 2001.
- Gwatkin, D. R. and Guillot, M.: *The burden of disease among the global poor*, World Bank, Washington DC, 1999.
- Joensuu, J., Koskenniemi, E., Pang, X. L., and Vesikari, T.: Randomised placebo-controlled trial of rhesus-human reassortant rotavirus vaccine for prevention of severe rotavirus gastroenteritis, *The Lancet*, 350, 1205–1209, 1997.
- Kerr, D. J., Dunn, J., Langman, M., and the Victor trial group: Rofecoxib and cardiovascular adverse events in adjuvant treatment of colorectal cancer, *N. Engl. J. Med.*, 357(4), 360–369, 2007.
- Kourilsky, P. and Viney, G.: Rapport au premier ministre sur le principe de précaution, Paris, octobre 1999.
- Kourilsky P.: L'éthique du Nord sacrifie les malades du Sud, *Southern Patients Sacrificed to Northern Ethics*, *Le Monde* Feb 8th 2004.
- Kramarz, P., France, E. K., and Destefano, F.: Population-based study of rotavirus vaccination and intussusception, *Pediatr. Infect. Dis. J.*, 20, 410–416, 2001.
- Kriebel, D. and Tickner, J.: Reenergizing public health through precaution, *Am. J. Public Health*, 91(9), 1351–1355, 2001.
- Lasser, K. E., Allen, P. D., Woolhandler, S. J., Himmelstein, D. U., Wolfe, S. M., and Bor, D. H.: Timing of new black box warnings and withdrawals for prescription medications, *JAMA*, 287, 2215–2220, 2002.
- Longini Jr., I. M. and Halloran, M. E.: Strategy for Distribution of Influenza Vaccine to High-Risk Groups and Children, *Am. J. Epidemiol.*, 161(4), 303–306, 2005.
- Martuzzi, M.: The precautionary principle: in action for public health, *Occup. Environ. Med.*, 64, 569–570, 2007.
- Mathers, C. D. and Loncar, D.: Projection of global mortality and burden of disease from 2002 to 2030, *PLoS Medicine*, 3, 11, 2011–2030, 2006.
- Melton, L.: Lifesaving vaccine caught in an ethical minefield, *The Lancet*, 356, 318–319, 2000.
- Miller, M. A. and Mc Cann, L.: Policy analysis of the use of hepatitis B and rotavirus vaccines in national immunization schedules, *Health Econ.*, 9, 19–35, 2000.
- Murphy, T. V., Gargiullo, P. M., and Massoudi, M. S.: Intussusception among infants given an oral rotavirus vaccine, *N. Engl. J. Med.*, 344, 564–572, 2001.
- Murphy, B. R., Morens, D. M., Simonsen, L., Chanock, R. M., La Montagne, J. R., and Kapikian, A. Z.: Reappraisal of the association of intussusception with the licensed live rotavirus vaccine challenges initial conclusions, *J. Infect. Dis.*, 187, 1301–1308, 2003.

- Psaty, B. M. and Kronmal, R. A.: Reporting mortality findings in trials of rofecoxib for Alzheimer disease or cognitive impairment: a case study based on documents from rofecoxib litigation, *JAMA*, 16, 299(15), 1813–1817, 2008.
- Ross, J. S., Hill, K. P., Egilman, D. S., and Krumholz, H. M.: Guest Authorship and Ghostwriting in Publications Related to Rofecoxib: A Case Study of Industry Documents From Rofecoxib Litigation, *JAMA*, 299, 15, 1800–1812, 2008.
- Sackett, D. L., Rosenberg, W. M. C., Muir Gray, J. A., and Haynes, Richardson, S.: Evidence-Based medicine: what it is and what it isn't, *BMJ*, 312, 71–72, 1996.
- Simonsen, L., Morens, D. M., Elixhauser, A., Gerber, M., Van Raden, M., and Blackwelder, W. C.: Effect of rotavirus vaccination programme on trends in admission of infants to hospital for intussusception, *The Lancet*, 358, 1224–1229, 2001.
- Strom, B.: How the US drug safety system should be changed, *JAMA*, 295, 2072–2075, 2006.
- Thompson, W. W., Shay, D. K., Weintraub, E., Brammer, L., Cox, N., Anderson, L. J., and Fukuda, K.: Mortality Associated With Influenza and Respiratory Syncytial Virus in the United States, *JAMA*, 289, 179–186, 2003.
- Tucker, A. W., Haddix, A. C., Bresee, J. S., Holman, R. C., Parashar, U. D., and Glass, R. I.: Cost-effectiveness analysis of a rotavirus immunization program for the United states, *JAMA*, 279, 1371–1376, 1998.
- Vesikari, T., Matson, D. O., and Dennehy, P.: Safety and efficacy of a pentavalent Human – Bovine (WC3) reassortant rotavirus vaccine, *N. Engl. J. Med.*, 354(1), 75–77, 2006.
- Wadman, M.: Regulator under siege, *Nature*, 20, 450(7173), p. 1143, 2007.
- Victoria, C. G., Wagstaff, A., Schellenberg, J. A., Gwatkin, D., Claeson, M., and Habicht, J. P.: Applying an equity lens to child health and mortality: more of the same is not enough, *The Lancet*, 362, 233–241, 2003.
- Wejner, C.: The future of research into rotavirus vaccine. Benefits of vaccines may outweigh risk for children in developing country, *BMJ*, 321, 525–526, 2000.
- Zambon, M.: Ethics versus evidence in influenza vaccination, *The Lancet*, 364, 9452, 2161–2163.
- Web sites**
- About EMEA structure: <http://www.emea.europa.eu/htms/aboutus/emeaoverview.htm> and <http://www.webcitation.org/5Yz8KZstJ>, last access: 1 July 2008.
- Sequence of Events with VIOXX, since opening of IND: <http://www.fda.gov/OHRMS/DOCKETS/AC/05/briefing/2005-4090B1.04.E-FDA-TAB-C.htm> and <http://www.webcitation.org/5Yz8VV9LG>, last access: 1 July 2008.
- Statement on influenza vaccine supply needs, J. L. Goodman, M.D., M.P.H. Director, Center for Biologics, Evaluation and Research, 4 May 2005, Before the Committee on Energy and Commerce United States House of Representatives, <http://www.fda.gov/bbs/topics/news/2005/NEW01160.html> and <http://www.webcitation.org/5Yz7nqXMI>, last access: 1 July 2008.
- CDC Testimony, 10 February 2005 on US Influenza Supply and Preparations for the Future before The Committee on Government Reform United States House of Representatives, <http://www.hhs.gov/asl/testify/t050210b.html> and <http://www.webcitation.org/5Yz4uCIQx>, last access: 1 July 2008.
- WHO World Health Report 2007: <http://www.who.int/whr/2007/chapter1/en/index.html> and <http://www.webcitation.org/5Yz4NP83K>, last access: 1 July 2008.
- NIAID, Oral Vaccine Protects Infants from Severe Rotavirus Diarrhea First Success in a Developing Country: <http://www3.niaid.nih.gov/news/newsreleases/1997/rotavirus.htm> and <http://www.webcitation.org/5YzHIgSUn>, last access: 1 July 2008.
- US Department of Health and Human Services: <http://www.hhs.gov/news/press/2006pres/20060504.html> and <http://www.webcitation.org/5Yz3dSerh>, last access: 1 July 2008.
- Sanofi-Aventis press releases: http://en.sanofi-aventis.com/press/ppc_18636.asp and <http://www.webcitation.org/5Yz3ar23n>, last access: 1 July 2008.
- WHO: Report of the meeting on future directions for rotavirus vaccine research in developing countries, Geneva, 9–11 February 2000, www.who.int/vaccines-documents/, 2000.