

International pharmaceutical social risk regulation: An ethical perspective

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Pharmaceutical production and distribution constitute big business. For the companies the rewards can be substantial. Rates of return on drug company investments tend to be higher than many other manufacturing enterprises. But reward is only one side of the story. There is also the issue of social risk, the focus of this article. Social risk for pharmaceutical production is especially pronounced. An ineffective or, worse, dangerous drug, can have dire consequences for the population at large. For this reason, there is elaborate government regulation and oversight of drug safety and risk. These systems, especially in the US and Europe, will be the main focus of this paper. The two systems will be described, and then compared and contrasted in terms of their framing of social risk and actions governments take to limit it. Systems elsewhere, especially in the developing world, are increasing in relative importance and these will be briefly discussed as well. Ethical issues that have arisen in these various systems will be surfaced and analysed. The paper will close with some conclusions and suggestions for further research.

Keywords: risk, externality, pharmaceutical industry, drug regulation, social risk, drug policy, ethics, corporate social responsibility

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The worldwide pharmaceutical industry has two major bases of consumption and production globally: the United States and Europe. In 2004 the US comprised roughly 45 % of the pharmaceutical market worldwide, while Europe comprised about 25 % (1). In 2006, global spending on prescription drugs topped \$600 billion with the US accounting for \$252 billion of the total annual sales (42 %). However, sales in it and the other nine biggest markets grew by only 5.7 %. Emerging markets such as China, Russia, South Korea and Mexico outpaced those markets, growing a whopping 81 % (2).

Clearly, pharmaceutical production and distribution constitute big business. For the companies the rewards can be substantial. Rates of return on drug company investments

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tend to be higher than many other manufacturing enterprises. As an example, various studies indicated that US drug companies earned approximately 15 % on their investments during the 1990's, a roughly 4 % 'excess' rate of return and much higher than the average 4 % return earned by Fortune 500 companies during the same decade (3).

But reward is only one side of the story. Drug companies take significant business risks in the form of R&D and uncertain effectiveness and success of any given medication. Companies in the industry spend proportionately much more on R&D than firms in other industrial sectors and their profits tend to be generated by relatively few products in their overall portfolios (3).

There is also the issue of social risk, the focus of this article. Most products have some sort of 'externality' in the form of costs borne by society but not by the manufacturer, *e.g.* pollution. Social risk for pharmaceutical production is especially pronounced. An ineffective or, worse, dangerous drug, can have dire consequences for the population at large.

For this reason, there is elaborate government regulation and oversight of drug safety and risk. These systems, especially in the US and Europe, will be the main focus of this paper. The two systems will be described, and then compared and contrasted in terms of their framing of social risk and the actions governments take to limit it. While for the moment the US and European regulatory and risk management systems are the most important in terms of overall production, systems elsewhere, especially in the developing world, are increasing in relative importance and these will be briefly discussed as well. Ethical issues that have arisen in these various systems will be surfaced and analysed. The discussion will close with some conclusions and suggestions for further research.

PHARMACEUTICAL SOCIAL RISK REGULATION IN THE UNITED STATES

The US drug safety and risk management process is managed at the level of the US federal government with the primary regulatory agency being the US Food and Drug Administration (FDA). In the US system of divided executive-legislative authority, the FDA is responsible for carrying out policy dicta as contained in legislation passed by the US Congress. The most pertinent laws here are the 1906 Pure Food and Drug Act which created that agency and subsequent acts which extended its powers over prescription drugs.

Pharmaceutical social risk management can be generally divided into premarket and postmarket safety regulation. The premarket approach emphasises testing of a given drug before it goes to market. If the drug 'passes' the required safety tests, it can go to market. The postmarket approach emphasises actual outcomes once a drug has entered the market and gained widespread use. Obviously, the two are not mutually exclusive, but one can be emphasised over the other.

The US drug safety regulatory system is heavily focused on premarket safety in which drug companies are required to conduct a series of increasingly large preclinical studies subject to FDA oversight until it can be established that the drug will have the intended

desirable effects with minimal unintended undesirable effects. Only at that point can the drugs be marketed and administered to the general public by prescription (4).

This system has been criticised on a number of fronts. Not least is the fact that the system is very expensive for drug companies developing new drugs. The consulting firm Bain & Company has estimated that the cost of discovering, developing and launching a new drug was nearly US\$1.7 billion in 2003 (though these included all expenses, such as marketing, and not just those associated with testing and other risk management expenditures) (5). Because of this high expenditure, as well as the long-lead times and uncertain outcomes of clinical trialling, it has been argued that drug development in the US tends to be focussed on 'blockbuster' drugs that will make high profits, possibly to the detriment of other drugs with lower payoffs but possibly higher public health benefits.

The effectiveness of this system from a safety point of view has also been questioned. The number of subjects in pre-market trials is necessarily limited, so if say, 500 people are tested without any adverse effect and the drug then goes to market, it is still quite possible that 1 in 1000 adverse effects might be missed, only to appear after the drug is introduced for general use. Even with a good clinical trial process, in the US »51 % of drugs have label changes because of major safety issues discovered after marketing; 20 % of drugs get new black box warnings after marketing; and 3 % to 4 % of drugs are ultimately withdrawn for safety reasons... Yet, when such safety problems have an incidence of less than 1 in 1000, they do not reflect a failure of the premarketing testing system, but are predictable. Indeed, previously unknown serious but rare adverse events from drugs continue to be identified long after they are marketed (*e.g.*, acetyl salicylic acid and Reye syndrome)« (6).

What this suggests is that (1) unanticipated adverse reactions to a drug are never going to be entirely avoidable even with substantial and high quality premarket testing, and (2) postmarket monitoring of drug reactions is perhaps worthy of more emphasis because this is where many problems are, in fact, discovered and this phase of the product lifecycle should be more structured. Postmarketing studies are currently optional in the United States and the FDA »lacks clear and effective processes for making decisions about, and providing management oversight of, postmarket safety issues«. The office within the FDA with primary responsibility for postmarket safety is the Office of Drug Safety (ODS), but it has little independent authority of its own, serving mainly as a consultant to the much more premarket focused Office of New Drugs (OND) (4).

Thus many in the US are calling for more postmarket monitoring and regulation. An expert panel of the National Institute of Medicine (part of the US National Academy of Sciences) recommended »that Congress ensure that FDA has the ability to require such postmarketing risk assessment and risk management programs as are needed to monitor and ensure safe use of drug products. These conditions may be imposed both before and after approval of a new drug, new indication, or new dosage, as well as after identification of new contraindications or patterns of adverse events. The limitations imposed should match the specific safety concerns and benefits presented by the drug product«. (7, Recommendation 5.1). The report also called for establishment of performance goals for safety over the product lifecycle; increased enforcement authority for the FDA; and mandatory reporting of premarket trial results (currently voluntary).

Others have been more forceful in calling for change. One author has called for the scaling back of premarket testing (the current trend is for regulators to expand the num-

ber of preclinical trials and number of trial participants) to be replaced by mandatory postmarket studies, with an initial postmarket period carrying only conditional approval of the drug by regulators for limited prescriptions with full warnings to patients that postmarket studies have not been completed. Only after satisfactory completion of the postmarket conditional trial would there be full drug approval. A schematic presentation of the current and trend US drug risk management model and this proposed change to it is provided in Fig. 1.

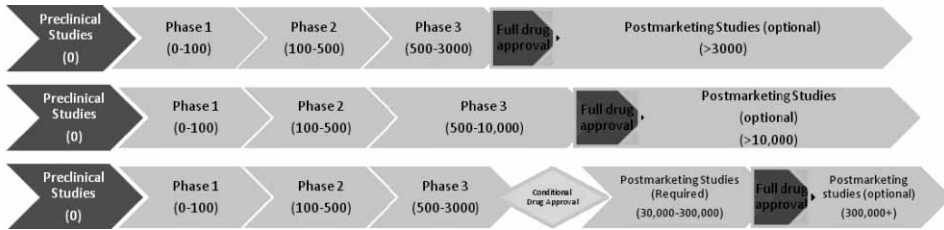


Fig. 1. Alternative models for studying drug safety: top – traditional model, middle – evolving model, bottom – proposed model. Numbers in parentheses indicate the number of study participants. Adapted from ref. 8.

REGULATION OF PHARMACEUTICAL SOCIAL RISK IN EUROPE

European drug risk management has been taking a somewhat different trajectory. »European« in this context refers to the frameworks issued by the European Union. Obviously, there are many individual country regulations within Europe still in the process of being harmonised. Here, a principle garnered from environmental risk analysis is gaining currency, namely 'the precautionary principle'. One author argues that »Whereas traditional risk assessment is best applied to situations characterised by risk, its proponents assert that the precautionary principle is needed to address uncertainty, ambiguity and ignorance«. Risk is defined as a condition where it is possible to define both the set of possible outcomes and the probabilities associated with each member of that set, whereas the other conditions – uncertainty, ambiguity and ignorance – have progressively fewer defined dimensions, with ignorance being the extreme case of not knowing either the possible outcomes or, necessarily, their probabilities. A scheme for the four possible conditions is laid out in Fig 2.

Knowledge about likelihoods	Knowledge about outcomes	
	Outcomes well defined	Outcomes poorly defined
Some basis for probabilities	Risk	Ambiguity
	Incertitude	
No basis for probabilities	Uncertainty	Ignorance

Fig. 2. Knowledge about likelihoods and outcomes: for possible conditions. Adapted from ref. 6.

The European Commission in 2000 recognised the principle in a guideline stating that where [regulatory] action is deemed necessary, measures based on the precautionary principle should be, *inter alia*:

- proportional to the chosen level of protection,
- non-discriminatory in their application,
- consistent with similar measures already taken,
- based on an examination of the potential benefits and costs of action or lack of action (including, where appropriate and feasible, an economic cost/benefit analysis),
- subject to review, in the light of new scientific data, and
- capable of assigning responsibility for producing the scientific evidence necessary for a more comprehensive risk assessment (8).

The basic thrust of the precautionary principle, and regulations such as those which attempt to implement them, is that there should be a presumption in favour of protecting the public good (however defined) instead of presuming that proposed actions (such as new drugs) are 'innocent until proven guilty'. This is in contrast to the notions of risk analysis, which takes a more neutral stance towards innovations of various sorts, implicitly holding that benefits and costs need to be (and can be) measured first before deciding to reject or accept a given option.

This principle has not yet taken widespread hold in European regulation of pharmaceuticals, though it is used, and was developed first in environmental regulation. The precautionary principle is quite conservative in that it effectively asks that »no harm be done« but that, of course, it is one of the main objections to be made to it, namely that scientific innovation may be impeded by its application. Also, there may be profound unintended consequences where an application of the principle might result in holding on of old and harmful technologies. Additionally, the principle is generally quite vague in its application.

A NOTE ON THE DEVELOPING WORLD

Already mentioned is the fact that the fastest growth in pharmaceuticals is not in America or Europe but in developing countries. A detailed review of social risk management in these markets is outside the scope of this limited review but of obvious importance to policymakers going forward simply because so much growth is occurring in those markets.

For example, in 1998, the US State of Connecticut spent more on health than the 38 low-income countries of sub-Saharan Africa combined. However, middle-income developing countries had a greater share than low income countries. The Pharmaceutical Research and Manufacturers of America (PhRMA) estimated that in 1998 7 % of their total markets were in Southeast Asia and China, and 7.5 % were in Latin America (9).

Since then, the developing world, middle-income countries in particular, have grown in relative importance as their share of world output and consumption grows. In particular, countries like India, Israel, Thailand, Brazil have developed significant domestic

pharmaceutical industries, some of which have become international producers. An Israeli company is now one of the twenty largest pharmaceutical corporations worldwide in terms of sales and two Indian companies rank in the top fifty (10).

Of course the, 'developing world' consists of multiple national markets with varying degrees of risk regulation that differ significantly from one another. This would suggest that there are a significant number of new fronts, so to speak, which need to be considered in social risk regulation.

However, the dominant market positions are still held by American and European producers, who develop and supply most of the significant drugs worldwide. Developing world firms are typically developing generic or specialised versions of medicines that have already been subject to American or European government oversight. Additionally, domestic sourcing is often not the issue so much as obtaining supply directly from foreign multinationals at prices affordable to developing world users. Nonetheless, the trend is clear: pharmaceutical social risk management is rapidly becoming variegated.

THE ETHICS OF SOCIAL RISK REGULATION REGIMES FOR MEDICINES

Having described some of the issues surrounding the efficacy of various social risk regulation regimes, one may ask a more normative question: are these regimes 'moral' or 'ethical' in their content and outcomes?

What is »ethics«? One source holds ethics to refer to a standard of behavior, a conception of right or wrong conduct (11). Fine so far as it goes, but it must be asked: what are the sources of »right« and »wrong«?

»Right« and »wrong« are concepts that fall under the rubric of morality, which a dictionary definition rather circularly holds to be »the degree of conformity of an idea, practice, *etc.*, to moral principles« (12). A little bit more helpful is the definition of »moral«, which is »concerned with accepted rules and standards of general conduct« (12).

Thus, one can say that ethical principles are guides to moral or immoral behaviour and morality itself defines what is »right« and what is »wrong«. Business ethics, meanwhile, is simply the application of the foregoing ideas to business settings.

Where fundamental moral and ethical definitions come from has been a topic of philosophical debate for thousands of years. Two basic approaches that form the basis for ethical thinking are deontology, which embodies the view that ethical decisions follow absolute principles (*i.e.*, that actions are inherently right or wrong, regardless of their consequences, an approach most famously associated with the philosopher Immanuel Kant); and consequentialism, which bases its judgment of any action on the goodness of its consequences (13).

This brief conceptual discussion by itself surfaces one salient fact: social risk regulation of medicines is rather fundamentally consequentialist rather than Kantian. Both EU and American drug policies speak explicitly of outcomes, and regulations are designed to maximise the occurrence of 'positive' outcomes and minimise the occurrence of 'negative' outcomes.

Indeed, the thorniest part of many ethical analyses, namely, choosing an ethical standard, may be most straightforward with social risk regulation of medicine. Medicines, after all, are designed to improve health and reduce disease and these are very clear benchmarks against which to design social risk management policies. Clinical trials are intended to surface efficacy (does the product achieve the positive health benefits claimed for it?) and unintended consequences (generally answering the question of whether the product results in harm to the user, though trials do sometime reveal unexpected positive side benefits). Indeed, the very purpose of medicine is outcome-based: it has no particular meaning or significance otherwise.

If one can safely assume a consequentialist frame for ethical analysis, the next normative question is whether current social risk regulatory regimes are achieving maximum benefit and minimum cost.

One could break this question into two parts: conceptual integrity and implementation integrity. On the conceptual front, a key ethical concern with American pharmaceutical regulation centres on its premarket bias. Clearly, there are significant problems with such a bias in that most negative drug effects are revealed after they are widely prescribed and used rather than before. Closer monitoring of postmarket drug effects has been loudly called for in the US for this very reason.

The general European approach (here referring to the EU rather than specific variations within European nations) recognises this problem implicitly with its precautionary principle. In a certain sense, this principle is an explicit rebuff to the notion that drugs, even drugs heavily tested in the premarket phase, are 'innocent until proven guilty'. In fact, the precautionary principle assumes that 'foreign' human-made and human-introduced substances must be assumed to cause harm unless there is very good reason to assume otherwise. US figures that show upward of 180,000 pharmaceutical induced deaths annually perhaps illustrate the wisdom of such caution (though some of these deaths are due to improperly administered drugs rather than defects in the drugs themselves) (14).

Of course, in consequentialist systems there are benefits and costs: drugs cause harm but they also deliver benefit and, clearly, for many types of drugs many more are saved than are hurt. A broad consequentialist measure of 'greatest good for the greatest number' probably indicates that current social risk regulation regimes are net positive, though perhaps with significant room for improvement. But society may have concerns about 'innocent' victims, young, poor, disadvantaged people and the like. Making distinctions between classes of people is obviously contentious but there are often underlying concerns about unintended consequences, *i.e.*, that some users expecting positive results were 'betrayed' by negative consequences, perhaps deemed a worse wrong than a user who was faced with clear risks and benefits and made a conscious choice.

This segues into the implementation dimension. The precautionary principle sounds robust – but how does one actually implement it in such a way that useful drugs are not delayed or perhaps not introduced at all? Similarly, in the US, how would postmarket studies actually work? For example, would people in the general population be exposed to unknown risks and in large numbers? Beyond this, drug companies are known for being quite influential in the policy-making and medical communities, giving large donations in many cases to political leaders and providing many material benefits to doctors or other potential prescribers. Social risk regulations may be well-designed but some argue are skewed by factors such as these toward industry rather than general interests.

CONCLUSIONS AND SUGGESTIONS FOR FURTHER RESEARCH

A number of hypotheses are suggested by this brief review. First, social risk regulation of pharmaceuticals lends itself naturally to a consequentialist ethical framework. Indeed medicines are inherently bound up with positive outcomes, meaning little in a framework that ignores such outcomes.

Second, a broad 'greatest number for the greatest good' framework may be a good starting point when considering the design of overall social risk management systems. Indeed, current US and European debates seem very much to pivot on issues of gross benefit net of gross cost.

Third, below this gross level, a consequentialist framework will likely have to be more varied as specific scenarios are considered where some affected groups are deemed more or less important than others. For example, developing world populations in some cases may be deemed as having greater need than developed world populations in the distribution and pricing of a given drug.

Fourth, and related to the prior point, non-consequentialist values may well enter in for these specific cases (e.g., 'innocent' subjects should not be used in postmarket studies even if their use might yield greater benefits than would be otherwise realised). Of course, these value discussions will be highly charged.

Fifth, and finally with respect to future research, explicit benefit-cost ethical analyses might be desirable, both for overall risk management systems and in specific instances. There are many clinically based analyses of this sort but very few ethical analyses, even though ethical issues are, at least implicitly, often paramount.

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S A Ž E T A K

Međunarodni propisi o farmaceutskom društvenom riziku: Etičko gledište

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Proizvodnja i distribucija lijekova vrlo je unosan posao. Za djelovanje farmaceutskih tvrtki bitna je dobit. Financijska ulaganja i povrat investicija u farmaceutskoj industriji veći su nego u drugim djelatnostima. Ali profit je samo jedna strana priče. Postoji i veliki društveni rizik, o čemu će biti riječi u ovom članku. Društveni rizik u farmaceutskoj proizvodnji je posebno naglašen. Neučinkoviti, ili još gore, opasni lijekovi, mogu imati pogubne posljedice za cijelo stanovništvo. Zbog toga na državnoj razini postoji regulativa i nadzor nad sigurnosti i rizikom uporabe lijekova. Ti sustavi, posebno sustavi u SAD-u i Europi, u fokusu su ovog članka. Ta su dva nadzorna sustava opisana i uspoređena u svjetlu ograničavanja društvenog rizika i mjera koje vlade poduzimaju kako bi ih ograničile. Drugi sustavi, posebice u zemljama u razvoju, dobivaju sve više na značaju i ukratko su opisani. Prikazani su i analizirani etički principi u drugim sustavima. Rad završava sa zaključcima i prijedlozima za daljnja istraživanja.

Ključne riječi: rizik, objektivnost, farmaceutska industrija, regulativa lijekova, društveni rizik, politika lijekova, etika, kolektivna društvena odgovornost

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