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Formulating an Ethics Agenda for Drug Development, Regulation, and Utilization

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Abstract

An Invitation: The time has come to examine the ethical dimensions of our pharmaceutical and device enterprise more broadly.

In this inaugural edition of Therapeutic Innovation & Regulatory Science (TIRS), Lipworth et al have provided a useful introduction to ethical analysis, a framework to guide ethical discussions, and a possible research agenda around the ethical aspects of drug and device development and policy.

It may seem strange to be proposing that TIRS become the vehicle for the discussion of the ethical dimensions of policies on drug, device, and companion diagnostics development. But for too long our "industry" has neglected this dimension of our work, to the detriment of all stakeholders, most notably the patient/consumer.

All of us are aware that our standing as an industry has suffered, and most of us would dearly love to be recognized as part of a vital enterprise dedicated to improving human health, not only unsullied by scandals fuelling the perception of overriding self-interest but also free to explore new ways to contribute to society. We are excited that TIRS might become the forum in which new thinking will emerge through systematic ethical analyses of pharmaceutical and device policy and practice.

As Acting Executive Editor and Editorial Board members we hope that you, as a regulator, pre-clinical scientist, project manager, patient, clinician, health economist, or other stakeholder, will accept this invitation to become involved, and contribute to a stimulating and productive discussion about aspects of drug and device development that have been relatively overlooked heretofore.

Keywords: drug development, bioethics, applied ethics, philosophy of medicine

What Is Pharmaceutical Ethics, and What Effects Has It Had?

Bioethics has long been concerned about issues to do with the development, deployment, and use of medicines, but the sub-discipline of pharmaceutical ethics is relatively new. For the most part, pharmaceutical ethics has been concerned primarily with the workings of the pharmaceutical industry.1,2 Among other things, ethicists have criticized the industry for developing medicines that are likely to be commercially successful even if these do not address genuine unmet needs, carrying out research without due regard for the well-being of research participants, distorting the design and interpretation of research in order to produce more positive findings, withholding negative results from publication, overstating the costs involved in research and development in order to overprice medicines, misusing intellectual property laws, and engaging in ethically dubious marketing practices. Academics, clinicians, journal editors, regulators, and funding bodies have been

subject to similar criticisms, largely due to their perceived entanglements with the pharmaceutical industry when they have received funding for research, education, regulation, or other activities.3,4

These concerns have contributed to ever more stringent regulation in the form of, for example, rules about the conduct of clinical research (e.g., demands that clinical trials be registered prior to carrying them out and that all data be publicly available5), marketing practices (e.g., most countries ban direct-to-consumer advertising of prescription pharmaceuticals6 and "off-label" marketing of drugs for indications that have not received regulatory approval7), and drug pricing and patenting.8 There are also more demanding rules governing industry engagement with academic researchers, clinicians, regulators, and funding bodies.9

While few deny that pharmaceutical companies have acted unethically at times, it has also been argued that ethicists have focused too much of their attention on the perils of commercialization to the exclusion of other concerns. More generally, ethical criticisms and regulatory responses have failed to recognize the changing landscape of drug development and regulation, the complexities of the commercial world, and the heterogeneity of attitudes, values, and practices within industry. This, critics argue, has resulted in a situation in which responses to concerns about industry misconduct are not always underpinned by sound evidence of their likely effectiveness in reducing harm.10 For example, in recent times, there has been much focus on exposing relationships between academics and the pharmaceutical industry,9 but there is little evidence that transparency alone is sufficient to change behaviour or prevent harm to the public.11

What Place Should Ethics Have in Pharmaceutical Practice and Policy?

Those who wish to defend the pharmaceutical industry, or who are critical of the direction that pharmaceutical regulation has taken, might therefore be critical of pharmaceutical ethics. People with this view might argue that the discipline has little to offer those discovering, testing, regulating, marketing, or prescribing medicines and that ethical inquiry should be treated with scepticism.

However, we would argue against such a dismissive approach for two reasons. First, all of the processes that make up pharmaceutical innovation, including drug discovery, testing, regulation, marketing, and prescribing—even those that appear to be primarily technical—are actually value laden, and all decisions made about these processes have ethical implications. To give an example, a public body charged with making decisions about which medicines should be subsidized for patients needs to consider not only available scientific evidence and economic calculations but also the following12-16:

- How clinical outcomes should be prioritized: for example, whether to rank survival or quality of life, whether thresholds for outcomes should be set, how to measure and evaluate incremental benefits, and whether to consider patient-defined benefits;
- How clinical benefits should be balanced against economic costs: for example, how much we are prepared to pay for a particular outcome and what opportunity costs we are prepared to incur;
- How to weigh up and mediate the claims of different populations: for example, how to proceed when there is competition for resources between populations that vary in size (e.g., those with a rare disease vs those with a common disease), health status (e.g., those with a life-threatening disease vs those with apparently minor health problems), socioeconomic status, or access to alternative therapies; and
- How to assess the clinical and economic research methods that have been used to generate evidence about therapies: for example, what level(s) of evidence should be deemed privileged, how uncertainty should be dealt with, and how the relative merits of different technologies should be assessed when they do not have comparative outcomes.

These beliefs are, in turn, underpinned by even deeper beliefs, such as those about the goals of health care, social justice and equity, and the methods and goals of science.

These are fundamental questions, and our answers to these questions depend ultimately on what we think it means to live a good life and what we believe societies, including their health services, should provide. Only ethics can provide the reasoning tools and conceptual frameworks needed to formulate and answer such questions.

A second reason for having an ethical voice in pharmaceutical policy making is that ethics can help us to make use of data about stakeholder opinions and preferences. While stakeholder analyses are central to pharmaceutical policy making, they inevitably run into the classic philosophical difficulty that arises when we try to move from "is" statements (facts) to "ought" statements (ethics).17,18 In the context of policy making, the problem is that it is not easy to move from descriptions of stakeholder opinions and preferences (which are kinds of empirical "facts" or "is" statements) to normative policy decisions (which are "oughts"). Moreover, even if we could somehow overcome the fact-value problem, we would still have to contend with situations in which different stakeholders have conflicting opinions and preferences. While ethical analysis cannot overcome the fact-value problem, it does provide a set of frameworks for drawing together facts and values. These approaches, known collectively as "empirical bioethics," seek to incorporate both empirical data (such as data about stakeholder opinions) and normative theory into ethical reflection and decision making.19

Pharmaceutical practice and policy making can thus be enriched by ethics in 2 ways: First, ethics can be used to help us to reflect theoretically on the right and the good. Second, it can help us to make sense of empirical data, such as data about stakeholder opinions and preferences, and incorporate these data into policy decisions.

An Agenda for Pharmaceutical Ethics

So where should pharmaceutical ethics focus its attention, and how can ethics avoid contributing to simplistic or otherwise misguided pharmaceutical policy? First, we suggest that ethical analysis of pharmaceutical practice needs to avoid seeing commercialization as a purely negative force. In particular, more attention needs to be paid to the fact that medicine has always existed in a commercial environment and that the distinction between "academic" and "commercial" activities is no longer clear cut. Indeed, many universities and academic medical centres now position themselves as "partners" with private industry20 and do not necessarily demand, or even want, complete control over the design, conduct, or dissemination of research.21 These subtleties tend to be hidden in the somewhat polemical debates about the "evils" of the pharmaceutical industry and the importance of protecting the ethically pristine government-funded academic research environment.

Second, we suggest that ethicists need to recognize that the pharmaceutical industry is not the only force influencing pharmaceutical innovation. Other influences, which are in need of equal attention, include the following, for example22 –28:

- The impact of national and global financial contexts, notably the recent global financial crisis, on the amount of funding available for research and drug development in the public and private sectors;
- The globalization of clinical research and drug manufacturing, particularly to countries in Asia, Eastern Europe, and Latin and South America;
- Challenges to academic research and development, with universities and research institutions competing for limited government funding and increasingly forming "public-private" alliances with industry;

- Changing scientific paradigms such as the advent of “pharmacogenomics” in which drugs are designed not for whole populations but rather for subpopulations with particular genetic profiles;
- The increasing focus of drug development on chronic, complex, and etiologically multifactorial conditions (e.g., psychiatric and neurological disorders and cancers);
- Changes to national and international approaches to drug regulation and pricing, with an increasing focus on premarketing and post marketing risk assessment, health technology assessment, comparative effectiveness analysis, and alignment with test approval;
- Changing consumer expectations, with consumers and patient advocacy groups being increasingly interested in ensuring that the research agenda generates the products and clinical outcomes that matter to them; and
- The development of new information technologies and the increasing exploitation of large electronic and tissue databases.

While some of these issues might appear at first glance to be simply about evidence, technology, or economics, each of these forces is likely to affect pharmaceutical innovation in ethically relevant ways (both positive and negative), and each is likely to be viewed differently by different stakeholder groups. In other words, these are all “ethical” issues that require systematic ethical analysis.

Other topics requiring systematic ethical analysis relate to the development and deployment of different kinds of medicines, including the following: how to ensure equitable access to high-cost medicines (e.g., expensive biological agents) or to lower cost but still unavailable “essential” medicines in resource-poor environments, how to ensure that personalized medicines (and associated biomarkers) do not limit the availability of effective therapies to particular populations, how to promote the production of medicines for rare diseases (orphan drugs) and medicines for neglected populations (e.g., paediatrics, developing world populations), and how to promote the availability of generic and bio-similar medicines without stunting innovation. Various phases of the pharmaceutical innovation process could also be subjected to more systematic ethical analysis, including the ethics of research agenda setting; academic publication; drug, device, and companion diagnostics registration; pharmaco-vigilance; health technology assessment; and the production and uptake of clinical practice guidelines.

What Role Can Industry and Regulators Play in Developing Pharmaceutical Ethics?

It follows from the above that members of industry and regulatory bodies, along with consumers and clinicians, have much to gain from engaging with ethical ideas. To facilitate this, we invite members of DIA to express their interest in joining a Special Interest Area Community (SIAC) focused on pharmaceutical ethics. We would also like this journal to be a site for ethical analysis, reflection, and debate in the form of research articles, letters, editorials, and opinion pieces. To begin the conversation, we will be publishing a series of articles on ethical issues. It is our hope that people will engage around ethical questions concerning drug development, regulation, and utilization, particularly those that are often misunderstood or unexplored, such as what the costs and benefits of regulation really are, whether moves to increase transparency have improved practice or just confused it, and whether the policies and practices of industry and government are creating the environment in which we are getting the drugs we need.

Acknowledgments

The authors thank Dr Adil Shamoo of the University of Maryland School of Medicine for his contribution to conceptualizing this article.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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