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Could the Norms for International Radiation Protection Be a Model for Pharmaceuticals?

Daniel Serwer[1,*]

[1]School of Advanced International Studies, Johns Hopkins University, Washington, USA

[*]Correspondence should be addressed to Daniel Serwer, daniel@serwer.org

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Abstract

There is no international norm-setting mechanism for pharmaceutical registration. By contrast, the International Commission on Radiological Protection (ICRP) has been recommending widely respected norms for X-rays and radioactive isotopes in medical and other uses for almost a century. It does so with no legal authority on the basis of collaborative deliberations by a self-selected group that includes experts concerned about both health effects and the benefits of ionizing radiation. Such an "epistemic group" has advantages over the more usual adversarial processes. It can evaluate the scientific evidence more objectively, it can adapt more rapidly to technological progress, and it can judge benefits as well as risks. Forming such normative epistemic groups for at least some of the rapidly growing number of new pharmaceuticals would avoid duplication and contribute to harmonizing pharmaceutical registration worldwide.

Introduction

For almost the past 100 years, users of ionizing radiation have generally followed the recommendations of an international commission created to protect patients, physicians, workers, and the general public. Established in 1928 as the International Commission on X-ray and Radium Protection, it is now the International Commission on Radiological Protection (ICRP), a nongovernmental organization headquartered in Ottawa, Canada. Its current goal is "to protect people, animals, and the environment around the world from the harmful effects of radiation [1]." It does this by recommending both basic radiation protection norms (in the form of maximum permissible levels) and means of achieving them, as well as promulgating those norms and informing professionals on how to meet them. It is currently working on a revision of the basic radiation protection norms, the first since 2007 [2]. The ICRP is explicitly concerned with enabling the benefits of ionizing radiation as well as protecting against its risks. It operates on a few million dollars per year, much of it contributed by national and international organizations that benefit from its findings.

No such norm-setting mechanism exists for international pharmaceutical registration. Should it?

The International Regime for Radiation Protection

To answer that question, we need to consider in detail what generated the norm-setting mechanism for ionizing radiation and why it has proven useful [3]. The prime movers of this nearly century-long history are what international relations scholars today call "epistemic [knowledge-based] groups," specialists within them, potential challenges from other institutions, and public pressure. Those are the factors that drove the setting and tightening of international radiation protection norms from 1928 onwards. They encouraged the growth of a resilient international regime that still persists today with universal legitimacy, even if national implementation is sometimes incomplete. The norms set by this international epistemic community have allowed valuable technologies to be used without causing the kind of harm that might have led to prohibition or limitation of their continued use. The Commission has no legal mandate or strong institutional backing and lacks representation from many parts of the world. None of those factors has undermined its legitimacy and authority.

That said, the history of radiation protection is not limited to closed epistemic groups. It is replete with public concern as a driver of norm-tightening. The professionals often tried to

insulate themselves and consistently denied its efficacy, but when public concern found resonance among professionals its impact was palpable. That resonance was often associated with moments in which new data became available or norm-setters thought they might face competition from other professional bodies. Specialists inside the world of radiation protection were particularly effective in advocating for tighter norms. Physicists in medical radiology after World War I and geneticists in radiobiology after World War II had an outsized influence on the course of radiation protection, as did professional radiation protection experts from the 1970s on. Endowed with more prestige than general practitioners and better represented at international meetings, specialists collaborated to tighten norms to levels they thought necessary to protect human health while allowing high-value applications to be implemented.

Knowledge-based norm-setting in radiation protection however did not start with norms. It started with reproducible measurement of doses and scientific investigation of effects. Radiation protection norms pre-World War I were inadequate because little was understood about how to accurately assess exposure or the biological effects of X-rays and radium, the very nature of which was disputed in the early years. Clinical medicine that claimed to be scientific in fact had little basis in contemporary science. The measurement of X-rays and radium was a matter of significant dispute into the 1930s. Without scientific dosimetry and knowledge of the genetic and carcinogenic effects of ionizing radiation, norm-setting before World War II was at best limited to avoiding, with a margin of safety, the more easily observable harm to skin, blood-forming organs, and the lens of the eye. The norms were more often too loose than too tight, judging (with the benefit of hindsight) from the subsequent tightening by more than an order of magnitude.

History Cannot Be Repeated

The detailed history of the International Commission on Radiological Protection cannot be repeated. Pre-World War I, only national radiation norms protected both medicine and society, enabling X-rays to be used for diagnostic and therapeutic purposes while protecting physicians and patients only from the most obvious harms. After World War I, pressure on the medical profession from physicists prompted the creation of international norms that enabled not only X-rays but also radium to be used extensively in medicine, though failure to apply the norms in specific industries harmed radium dial painters and uranium miners. Those tragedies heightened sensitivity to radiation effects. During World War II and for a year thereafter, tens of thousands of Manhattan Project workers fabricated the deadliest weapons known while observing the international norms developed for different purposes, with only a few acute incidents and no perceptible health impact on tens of thousands of other employees.

Thereafter, the ICRP norms protected the many applications of radioisotopes and an entirely new industry using nuclear reactors to produce electricity. While in some countries that industry has been closed or is phasing down, that is because of the risk of accidents rather than the routine environmental effluents the international norms sought principally to control. Radiation protection concerns among the general public also helped to generate pressure for an end to nuclear weapons testing in the atmosphere, which has proven unnecessary for weapons development. Even states that have never ratified the relevant treat have adhered to that prohibition.

None of these specific contingencies is likely to be repeated for other technologies.

Available Lessons from That History

The right lesson from radiation protection is that any norm-setting process for a new technology should have a firm basis in assessment of doses and effects, including both risks and benefits. Optimization requires that both be considered in many applications. This assessment need not be entirely divorced from industry or government. There is far more likelihood that governments and industries will agree with scientific experts on doses and effects than on norms. But even if they have different utility functions for the technology in question, norm-setting will be better informed if industry and government contribute their own knowledge and can agree with experts on doses and effects. The international group establishing the norms in the case of ionizing radiation was and still is nongovernmental, but that is not a necessary feature. Norm-setting by governments and intergovernmental organizations is today more the rule. Still, the basic mechanisms at work in radiation protection are worth notice. International norms can be set to establish a basis or limits for competition, with specialists playing a stronger role at the international level than they can at the national level, where they are outnumbered and where economic considerations are likely stronger.

Any such effort should anticipate and welcome public criticism and input, as the radiation protection regime eventually did. It is an essential ingredient in ensuring that the process moves forward. Much as scientists may have good reason to doubt how much the public really understands, the professional institutions dedicated to radiation protection would not have moved as far and fast as they did without pressure from insurance companies, the courts, public hearings, the media, public protests, and other fora for expression of concern. The national and international institutions concerned with radiation protection tried for many decades to seal themselves off from politics and public scrutiny and denied their influence. As a result, the epistemic groups ran the risk of losing control of the norm-setting process, which at various points might have passed to other professional organizations or governmental institutions. Opening the institutions to more public scrutiny

and input, and to wider geographic diversity in the case of the international institutions, has not hurt their authority.

The main norm-setting mechanisms in the case of radiation protection were epistemic groups in key countries developing the technology and seeking to use it in medicine, industry, and weaponry. These groups, both at the national and international levels, were interdisciplinary and included people with interests in radiation applications as well as those studying its physical and biological effects. They sought not to block the use of technology, but rather to enable its use by limiting its negative impacts on human health and eventually also the environment. Swedish physicist Rolf Sievert put it this way in 1958 while chairing the ICRP for the second time:

"I will begin by defining the establishment of maximum permissible radiation levels as a non-scientific task which must primarily be based on scientific knowledge and judgement. It must be carried out independently of the demands of persons or organizations who are responsible for the increase of ionizing radiation in the world, but nevertheless in close contact with them."

He elaborated:

"The only way to arrive at useful and well balanced maximum permissible levels seems then to be to bring people together representing extensive knowledge and experience on the one hand of the relevant biological effects, and on the other, on the working conditions and protections possibilities. Such a group is capable of discussing the fundamental protection problems from the various aspects relevant for establishment of sound principles in the assessment of maximum permissible levels [4]."

This mixture of interests in our contemporary world is often frowned upon. Regulators, it is believed, need to be separated from the industry regulated. Many standard-setting processes in today's world are adversarial, not cooperative. Those for and against a particular standard argue for their respective perspectives in administrative, judicial, or political proceedings. Proprietary data is often kept secret, lawyers and lobbyists make fortunes, and the connection of decisions to scientific data is obscured.

If your objective is science-based value judgments that will allow the use of risk-laden technology, there is good reason for people concerned about a particular technology to know and appreciate the people who want to use it. There is also good reason for the people using a particular technology to know and appreciate those who are concerned about it. Effective advocacy in both directions requires epistemic depth, mutual understanding, and competent groups focused on providing normative solutions that protect the public as well as use of the technology. This process is akin to one psychologist Daniel Kahneman called "adversarial collaboration," which is a process he used to design definitive experiments to test conflicting psychological theories [5]. No such definitive tests resulted, but wider and better understanding did.

Pharmaceutical Regulation

Pharmaceuticals are not subject to international norms like those of the ICRP. Instead, national governments and the European Union regulate them. Pharmaceutical research and development are concentrated in the U.S. and Europe, just as radiation research and development was in 1928. U.S. regulation is centralized in the Food and Drug Administration (FDA), while the European Union approves pharmaceuticals and medical devices "through a network of centralized and decentralized agencies throughout its member states [6]." Both in the U.S. and in Europe the processes are more adversarial than collaborative. According to Gail Van Norman, the FDA review process for pharmaceuticals in 2016 was generally a bit quicker than the centralized European one administered by the European Medicines Agency (EMA), but most European applications are submitted at the member state level in more than one of the 27 member states, rather than to the EMA. Companies applying to register pharmaceuticals are responsible for development costs but many clinical trials are sponsored by government agencies, all the data from which is available to the public in principle in the U.S. but not in Europe, if it is unpublished. The regulatory processes in both Europe and the U.S. are essentially adversarial, not cooperative.

Despite the trans-Atlantic differences, there is widespread recognition of the importance for pharmaceuticals of safety and effectiveness as well as the need to bring medically beneficial innovations quickly into use. No one in the industry, the scientific community, or government regulatory authorities will want to forget the thalidomide disaster, but even thalidomide has approved beneficial uses today [7]. Regulatory authorities, including those in the U.S. and Europe, have been trying to harmonize their processes through the nongovernmental International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, which "brings together regulatory authorities and pharmaceutical industry representatives to discuss scientific and technical aspects of drug registration." Established in 1990, it had issued by 2023 fifty-nine guidelines on salient issues in the categories of quality, safety, efficacy, and "interdisciplinary" intended to promote harmonization of registration processes, without however recommending specific registrations. The implementation of the guidelines in some countries is spotty, but strong in the U.S. and EU [8]. Pharmaceutical regulators also participate in an intergovernmental program that aims at regulatory convergence, a cooperative scheme among pharmaceutical inspectors with 52 participating authorities, and an "executive-level" forum of medicines regulatory authorities [9]. The U.S. and EU since 2019 have relied on each other's inspections for human medicines, and since 2023 for veterinary medicines, produced in their own territories. They thereby avoid duplicative work while cooperating in inspections in other countries [10].

The U.S. market for pharmaceuticals is about 49% of the world market, while Europe's is about 24% [11]. Not surprisingly, most of the rest of the world therefore follows the U.S. and European leads when it comes to regulation of many pharmaceuticals. Even if they have their own approval processes, they have to meet U.S. or EU standards if they have production facilities and want to export to these dominant markets, and many countries lack the expertise required to do the elaborate clinical trials and technological development required for pharmaceuticals on their own.

The FDA and EMA collaborate on inspections but have not collaborated on specific registrations, even if the existing executive-level meetings among regulatory authorities likely include some informal discussion of specific pharmaceuticals. There are high barriers to collaboration among the regulatory authorities, including national pride, commercial interests, diverse population genetics, differing regulatory systems, and cultural preferences. International epistemic groups to recommend norms for the safety and effectiveness of at least some pharmaceuticals could circumvent some of these hurdles and enable economies of scale both in research and development and in pharmaceutical distribution. Harmonization of registrations would reduce duplicative efforts and enlarge market availability. The rapidly growing number of pharmaceuticals being brought to market will increase pressure for some sort of international cooperation on norms in the future.

Modern technology can facilitate the formation of epistemic communities. The most dramatic example is the Intergovernmental Panel on Climate Change (IPCC) [12]. Though nominally an assembly of 195 of the world's governments, the IPCC is the United Nations body for assessing the science related to climate change. A core writing team of a few dozen people assembles its assessment reports from thousands of scientific contributions. This is an epistemic community of remarkable size, range, and diversity. In addition to its assessment, it helped enunciate and establish norms for global warming (1.5/2 degrees C above pre-industrial temperatures) that governments now mostly accept, however grudgingly and ineffectively. But those norms have in practice become the measuring sticks by which the world assesses progress, or lack thereof, on climate change.

Conclusions

Today national governments decide on pharmaceutical registrations in adversarial processes, based on scientific advice. The question is whether it would be preferable to base national decisions on the recommendations of a prestigious international epistemic group concerned with newly emerging pharmaceuticals, the number of which is increasing yearly. This would be an effort by leading pharmaceutical researchers and companies to put their own house in order by collaborating more deeply on doses and effects, with the aim of recommending registrations that might be applied worldwide. No formal intergovernmental arrangements would be necessary. Instead, governments and industry might learn to rely on the unfettered inquiry that characterizes "adversarial collaboration." Is it too much to ask that pharmaceutical regulation be based on the best available science, as determined by the best available scientists worldwide in a process open to the general public?

Declarations

Daniel Serwer is a professor at the Johns Hopkins School of Advanced International Studies and a senior fellow at its Foreign Policy Institute. This article is derived in part from his book, *Strengthening International Norms: The Case of Radiation Protection* (Palgrave MacMillan, 2024). Serwer blogs at www.peacefare.net and tweets @DanielSerwer.

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