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Round Table Discussion

Pharmaceutical R&D needs new financial paradigms

John H. Barton[1]

I endorse Professor Correa's sound recommendations on patent law. The patent system is at its most successful when it covers a significant discrete product or process. It is at its least successful when it covers something much broader or much narrower. Patents on broad scientific principles are generally bad, because in the words of the United States Supreme Court, they "may confer power to block off whole areas of scientific development, without compensating benefit to the public" (*1*). At the other end of the continuum, patents on very minor improvements create a monopoly out of proportion to the technological benefit of the improvement. Moreover, such patents may impose extensive and costly legal negotiations on those who wish to have the freedom to launch a new product. Thus, national patent offices should apply appropriate doctrines of utility or of the scope of patentable subject matter to avoid the problem of overly broad patents, and appropriate doctrines of inventive step to avoid the problem of overly incremental patents.

I want to emphasize that the patent law provisions that Correa describes are only part of a much larger body of issues affecting the balance between drug development incentives and drug access. In the United States, the 1984 Waxman–Hatch Act explicitly extends a drug's regulatory monopoly (with some very technical provisions that have been used to obtain longer exclusivity than was probably intended by Congress and have recently been revised). Relevant to middle-income countries with the ability to build a generic industry, the TRIPS Agreement and some other trade agreements restrict the right to use an original applicant's clinical trial data to obtain approval for a generic product. Far more important, however, is the issue of cost. For the poor and those in poorer nations, access to drugs at even generic prices is inadequate, as shown by the estimate of WHO's 3 by 5 initiative to make antiretroviral drugs available to 3 million people by 2005: at present only one person out of 15 people needing antiretrovirals in the developing world is actually receiving them. Solving the legal problems does not solve the more difficult financial problems.

Finally, the industry is facing an additional problem that Correa does not raise: the number of genuinely new pharmaceutical products being approved is falling even as the level of research investment by the pharmaceutical industry is growing rapidly. The reasons are not clear. One may be a decline in basic scientific opportunities, at least for the kinds of disease that are of most economic interest to the industry. Others may include higher costs of clinical trials or higher effective regulatory standards. Encouragingly, the area where the number of new products is increasing is that in which products derive from biotechnology. This overall declining pay-off of research is very

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important, and the industry may have to find new research paradigms. This is a concern for the world as a whole. In addition, if the industry is to develop products especially for the developing world, it will need new financial paradigms as well. ■

Conflicts of interest: none declared.

1. *Brenner v. Manson*, 383 US 519. United States Federal Supreme Court, 1966.

Patents do not strangle innovation, but their quality must be improved

Amir Attaran[1]

There is no doubt that the patenting of inventions — *any* inventions, not just medicines — is rising unprecedentedly. As Professor Correa writes, the resulting thicket of patents could "deprive society of the benefits [of] … widespread use and dissemination of basic scientific ideas".

Possibilities and facts are not the same thing, however, and there is surprisingly little empirical data to show that the patent thicket is subtracting from the rate of innovation or society's benefit from it. Maybe that is happening without anyone noticing, but the available evidence suggests otherwise.

Correa cites extensively from the NIHCM analysis of new medicines, 1989–2000. As he correctly points out, only 15% of the medicines approved in that period contained new active ingredients and were exceptionally medically useful. Fully 65% of medicines contained active ingredients that had been commercialized earlier, and 54% were "incrementally modified drugs" that bear great resemblance to already existing medicines.

But how do these statistics prove that innovation is being strangled to death? In fact they prove just the opposite: that innovation is alive and well. If an inventor's rational expectation is that, more likely than not, the difference between the new medicine and those before it will not constitute a great leap, but only an "incremental" improvement, and the inventor still ploughs money and time into its research and development, then innovation certainly does not seem strangled. Actually, it seems irrepressible.

This is not to say that Correa's hypothesis about patent thickets harming pharmaceutical innovation is necessarily wrong. Obviously, the more patents, the more inventors must spend on patent management, licensing and litigation. At some point, the mounting costs must dissuade inventors with shallow pockets more than those with deep ones, so that research and development accretes in major pharmaceutical companies, ahead of small biotechnology firms. The extent to which that accretion is happening, and if it leads to a net decrease in innovation, is under-researched and not clearly known.

Correa is correct that the quality of patent examination is scandalous. Even in Europe or North America, many dubious patents are issued. The resulting lack of legal certainty harms everyone: competitors who must spend heavily to overturn wrongly granted patents; consumers who pay a premium while those patents remain in force; and even companies and their shareholders, as happened when an invalid Prozac patent was finally overturned, wiping US$ 35 billion off Eli Lilly's market capitalization (*1*).

Ironically, among the least affected are the low- and middle-income countries. This is simply because the patenting of medicines there is rare — no more than a few percentage points for the *WHO Model List of Essential Medicines* (*2*). If Professor Correa is truly correct in the opinion that most new medicines "did not provide significant clinical improvement", then even a major push to patent all new medicines in developing countries would only modestly affect public health. There will always be a minority of cases where patents cause trouble — or maybe even harm — but as the hierarchy of concerns for developing countries goes, patents should not top the list. ■

Conflicts of interest: none declared.

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Pharmaceutical innovation is evolutionary and incentive-driven

Harvey E. Bale[2] & Boris Azais[3]

Professor Correa alleges that "lax rules on patentability and shortcomings in procedures" encourage non-inventive or "minor, incremental" drug developments and "strategic" patenting activities. He thus suggests that patents should not be granted on medicines that "do not entail a genuine therapeutic progress". This is to misread the nature and value of pharmaceutical innovation — as in all scientific sectors, the process is one of evolution and reflects the principle that "Nature does not make jumps".[a] Correa's policy prescription, based on an inaccurate diagnosis of the problem and a seriously flawed key study, would lead to contradictory and anti-innovation results for critically needed therapeutic innovation in major global disease threats.

Correa notes that public sector research provides important building blocks for private research and development, and that pharmaceutical companies invest "the largest part of global funds for pharmaceutical R&D". In modern drug development, equipped with an armamentarium of scientific and technical skills, the private sector manages the discovery and development processes in a competitive market that presents high risks of failure. The United States National Institutes of Health (NIH) reported in 2001 that of the 47 prescription drugs for which sales exceeded US$ 500 million per year, the NIH had contributed to the discovery or development of only four (*1*).

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[a] See Geoffrey Fishburn. *'Natura non facit saltum' in Charles Darwin and Alfred Marshall*. Available from: http://www.qut.edu.au/arts/human/ethics/ieps/absfish.htm

Incremental innovation responds to the needs of broader conditions of safety, efficacy, selectivity, and utility — which translate into significantly better health outcomes (*2*). Indeed, 50% of the drugs on the WHO Essential Drugs List are compounds introduced subsequent to the first in a therapeutic class, and 25% are approved (after additional clinical research) for therapeutic uses other than the initially approved indications, exemplifying that the future utility of medicines cannot be determined at the time of drug approval (*3*).

Correa does not cite a single example of minor, incremental innovation undeserving of intellectual property incentives. His critique of pharmaceutical innovation rests on a study by the National Institute for Health Care Management (NIHCM), an affiliate of the United States private health insurance industry, which has serious gaps in its methodology. For example, the NIHCM excluded all FDA approvals of vaccines and other biological products from its calculations: as a result, over 130 vaccines and biotechnology products are simply omitted.[a] Further, the NIHCM analysis is based on the FDA's priority review process, assuming that it translates into innovative products (versus those going through the standard review). Priority review is merely a managerial tool, which the FDA points out is "based on information available at the time application is filed [and] not intended to predict a drug's ultimate value" (*4*). The value of new medicines emerges most clearly once they have been introduced into medical practice.

Finally, Correa's proposal leads to the untenable situation that improvements on existing therapies would not be patentable. Breakthrough innovations (patentable) would thus face immediate generic copies of similar but more advanced compounds (not patentable). Facing non-patentability or immediate generic copying, what incentives would there then be for innovator companies to continue their enormous investments in developing new medicines? Therapeutic advances historically delivered by the private sector would cease without the protection of the patent system.[b] Some generic producers might benefit in the short term from such a temporary windfall, but in the end, neither they nor patients would experience a healthy future. ■

Conflicts of interest: none declared.

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Problems with patent examination in the developing world

Christopher Garrison[1]

Professor Correa illustrates clearly some of the concerns associated with contemporary R&D models and the patterns of patenting activity in developed countries that support them. He draws the proper conclusion that developing countries need to pay more attention to their patent examination and granting procedures if they are to avoid similar problems.

To develop this theme further, two steps must be considered. Firstly, developing countries must decide upon or review their rules on patentability, bearing in mind the degree of flexibility still available under the TRIPS Agreement; least developed countries need neither grant nor enforce patents for pharmaceutical products until 2016 (*1*). If a developing country wished to minimize the number of pharmaceutical patents that it must grant, it could adopt more restrictive (but still perfectly legitimate) interpretations of its TRIPS obligations than those adopted by Europe, Japan or the United States, and might thus avoid some of the problematic patents cited by Correa. Secondly, to make this work, developing countries must put in place a robust system to ensure that the rules they have chosen are observed. This is not a trivial task.

To examine rigorously a patent application requires a high degree of expertise: for example, the European Patent Office employs some 2500 trilingual patent examiners, many with postgraduate qualifications. A few developing country patent offices do have effective examination capabilities, if not on such a scale, but they are the exception rather than the rule (*2*).

Patent offices in many developing countries rely to a great extent on the work of the European, Japanese and United States Patent Offices. Through the Substantive Patent Law Treaty negotiations hosted by the World Intellectual Property Organization, these three Patent Offices are pushing for a further international harmonization of certain fundamental patentability requirements, largely along the lines of their own rules (*3*). Although adopting further harmonized international rules may mean that developing countries have to devote fewer resources to patent examination, by the same token they will further lose the policy freedom available under TRIPS to choose rules better suited to their needs. A regional approach might instead be taken if developing countries pool their resources through regional patent offices, such as the African Regional Industrial Property Office (ARIPO).

Whether as a result of choice or institutional resource limitations, it is quite common in the developing world not to carry out any substantive examination before granting a patent. This must be a serious concern in the light of the issues that Correa raises and the potential impact on access to medicines. Developing countries with such "registration" systems run the substantial risk of an asymmetric situation where it is relatively easy to get patents but relatively hard to challenge them,

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[a] See footnote 3 in the NIHCM study quoted by Correa. For a review of the NIHCM study and a list of some of the drugs excluded, see: http://www.phrma.org/publications/quickfacts/admin/2002-06-11.421.pdf

[b] The story of paroxetine hydrochloride, an antidepressant agent, is illustrative: first discovered and patented by Ferrosan in 1977, the anhydrate form of this molecule was not suitable for lack of stability. After an 11-year quest, Beecham of the United Kingdom (now GlaxoSmithKline) developed a different and more stable salt of the same active compound, leading to FDA approval in 1992. A different salt of the same compound might be discarded as a minor, incremental improvement compared with the discovery of the original active ingredient, but Beecham's discovery was in fact a crucial step to bring a new treatment to patients.

especially if it has to be done through the courts. Unlike in developed countries, it is rare for granted patents to be challenged in developing countries — one notable exception being the recent successful challenge of a didanosine patent in Thailand by Thai civil society groups (*4*).

It is therefore very important that Correa's call for further reflection on the examination, granting and administration of patents in developing countries is heeded, and that robust systems can be found to implement the necessary policies. ■

Conflicts of interest: none declared.

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