Round Table

Ownership of knowledge — the role of patents in pharmaceutical R&D

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Abstract Both the public and the private sectors contribute to research and development (R&D) in pharmaceuticals. The public sector originates many of the discoveries of new drugs. The private sector, which focuses on development, is heavily reliant on patents. Though patents are presumed to reward genuine inventions, lax rules on patentability and shortcomings in procedures permit protection to be obtained on a myriad of minor developments. These patents, though weak and possibly invalid in many cases, are used to restrain competition and delay the entry of generic competition. Developing countries should design and implement their patent laws so as to prevent strategic patenting and promote competition and access to medicines.

Keywords Patents/legislation; Pharmaceutical preparations; Research; Diffusion of innovation; Drug industry (*source: MeSH, NLM*).

Mots clés Brevet/législation; Préparations pharmaceutiques; Recherche; Diffusion des innovations; Industrie pharmaceutique (*source: MeSH, INSERM*).

Palabras clave Patentes/legislación; Preparaciones farmacéuticas; Investigación; Difusión de innovación; Industria farmacéutica (*fuente: DeCS, BIREME*).

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Voir page 786 le résumé en français. En la página 786 figura un resumen en español. يمكن الاطلاع على الملخص بالعربية في صفحة 786.

Although governments are responsible for a significant portion of global spending on research and development (R&D), since the 1980s a steep decline in the share of government funds for R&D is a trend common to all major industrialized countries and many other Organisation for Economic Co-operation and Development (OECD) countries. In the largest OECD countries (with the exception of Italy), the private sector performed between 62% and 70% of total national R&D (*1*).

Private and public sources also coexist in pharmaceutical R&D. The division of labour in pharmaceutical R&D between the two sectors is related, at least in principle, to the nature of the knowledge that is fostered (*2*). In most cases, the discovery of important new drugs is made by public institutions, which later license their development and exploitation to private firms. Some 70% of drugs with therapeutic gain were produced with government involvement (*3*). Basic research that led to the discovery of potential "drug leads" has almost always been publicly funded at universities, in-house government facilities, or research institutes in Europe, North America, and Japan. Since the beginning of the 20th century, publicly funded research has led to major drug lead discoveries in, for example, tuberculosis, other infectious diseases and cancer. More recently, publicly funded research has led to the discovery of antiretrovirals for the treatment of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). Publicly funded genome research has also produced many drug leads (*4*). In the United States, the federally funded biomedical research supported by the National Institutes of Health (NIH) plays a vital role in new drug development, feeding into the R&D activities of the private pharmaceutical industry that operates under patent protection (*2*). In addition to this direct and important contribution, governments of many developed countries grant tax credits and other incentives for R&D (*1*).

However, private industry invests the largest part of global funds for pharmaceutical R&D. Unlike the public sector, industry's research agenda is dominated by profit-making objectives. Most of industry's resources are concentrated on applied R&D, though funds are also devoted to basic research. In 1999, for instance, 24.5% of R&D spending was on basic research in the United Kingdom, 36% in the United States, and 18.4% in Canada (*5*).

Given the objectives and nature of industry's activities, they rely heavily on the acquisition and enforcement of patents worldwide. A common belief is that patents are normally acquired to protect *new* drugs, and thereby recover the substantial R&D investments made for increasing the range of available therapies; but the number of patents annually obtained to protect genuinely new pharmaceutical products is very small

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and declining, whereas thousands of patents are applied for or granted concerning pharmaceutical-related inventions. The number of patents acquired in relation to "upstream" inventions, that is, scientific discoveries rather than specific technical solutions, is increasing. This kind of patenting detracts from public domain knowledge that could be used "downstream" by many researchers to explore multiple inventive opportunities; it deprives society of the benefits that the widespread use and dissemination of basic scientific ideas could generate (*2*). The problems raised by this form of privatization of science have been explored by an extensive literature (*6*, *7*). Patents, on the other hand, are ordinarily acquired for a myriad of follow-on, merely incremental, or minor developments.

Innovation in pharmaceuticals

Innovation in pharmaceuticals relies increasingly on the knowledge gleaned from preceding innovations and on generally available techniques (*8*, *9*). As in other sectors, innovation "has shifted away from models based on absolute novelty and first improvement towards a model in which innovation is no longer driven by technological breakthroughs but by the routine exploitation of existing technologies" (*10*). Innovation in this sector follows, therefore, an essentially "cumulative" model of innovation, as opposed to the "discrete" model, where the prospects of variations and improvements of inventions are substantially bounded.

Many of the new chemical entities of pharmaceutical use do not entail a genuine therapeutic progress; they are "me too" drugs, developed as a result of the great deal of emulation of successful drugs undertaken by rival companies (*11*). Pharmaceutical innovation also includes a large number of improvements or minor changes to existing drugs, and the identification of new uses of known products. Incremental innovation is often motivated by the objective of extending the commercial benefits derived from existing products, particularly when original patents expire and new patents may be used to prolong market exclusivity.

According to a report of the National Institute for Health Care Management (NIHCM) in the United States, from 1989 to 2000 the United States Food and Drug Administration (FDA) approved 1035 new drug applications. Of these, a third (35%) were products with new active ingredients, or new molecular entities (NMEs). The other 65% used active ingredients that were already available in a marketed product. Over half (54%) were incrementally modified drugs, or new versions of medicines whose active ingredients were already available in an approved product. The rest (11%) contained the same active ingredient as identical marketed products (*12*).

Priority NMEs, the most innovative type of new drugs, were rare in the 12-year period 1989–2000: just 153 (15%) of all new drug approvals were medicines that used new active ingredients and provided significant clinical improvement. Drugs providing moderate innovation comprised another 28% of approvals. The other 57% of approvals were for drugs showing only modest innovation, at best: 46% made some modification to an older product containing the same active ingredient, while the remaining 11% were identical to marketed products. As a result, the NIHCM reports, priority NMEs — the most innovative drugs — contributed little to the increase in new products, and most growth came from products that did not provide significant clinical improvement, especially modified versions of older drugs (*12*).

Patenting cumulative innovations

The cumulative nature of innovation has important repercussions on the patent system. Though theoretically conceived to reward inventions marked by considerable originality, the patent system is plagued with grants covering incremental, minor — in some cases trivial — developments. They are not the product of inventive efforts, but rather the outcome of "taking a speedy path down a trail that was obvious to many" (*8*, p. 128). In 2001, the United States Patent and Trademark Office granted over 171 000 patents, almost twice the number granted ten years earlier. This increase cannot simply be attributed to an increase in R&D productivity, but to the flexibility of the patent system to permit the protection of follow-on and other developments (*13*, pp. 1933-4).

Moreover, there is increasing evidence about poor patent quality. (A poor-quality patent is one that is likely to be invalid or contains claims that are likely to be overly broad (*14*).) "Non-obviousness" or "inventive step" (one of the key patentability requirements) is assessed against a standard that many follow-on and routine innovations do not find difficult to meet, based on the fiction of what "a person with ordinary skill in the art" would have been able to derive from prior art. Weaknesses in patent procedures, in addition, favour the granting of patents over trivial or minor developments (*14*, *15*), despite the significant resources invested in developed countries to fund patent offices (*16*).

Large firms have rapidly learned how to exploit lax patentability standards and the shortcomings in the patent examination process. They apply different strategies to use patents offensively as means to encumber or block potential competitors. Thus, "*blanketing*" strategies aim at mining every step in a manufacturing process with patents claiming minor modifications; "*fencing*" refers to a situation where a series of patents blocks certain lines or directions of R&D; "*surrounding*" takes place "when an important central patent can be fenced in or surrounded by other patents, which are individually less important but collectively block the effective commercial use of the central patent, even after its expiration" (*17*); and "*flooding*" is based on the acquisition of many patents on minor or incremental variations on technology developed by another company (*18*, *19*). For other anti-competitive practices, see (*20*).

As noted by the NIHCM, "drug manufacturers patent a wide range of inventions connected with incremental modifications of their products, including minor features such as inert ingredients and the form, color, and scoring of tablets. In many cases, these patents discourage generic companies from trying to develop a competitive product" (*12*). Moreover, backed by substantial budgets for patent acquisition and litigation, pharmaceutical companies have been able to delay substantially the entry of generic competition by "evergreening" many of their patents (*21–23*). According to United States lawmaker Waxman (one of the authors of the United States Drug Price Competition and Patent Restoration Act of 1984, commonly known as the "Waxman–Hatch Act") brand-name companies "have used creative lawyering to try and extend the period of their monopolies long past the time intended by Congress" (*24*).

Poor-quality patents acquired to encumber or delay generic competition are generally aggressively used against competitors. They are likely to be invalidated totally or partially, however, if subject to a more serious scrutiny by judicial courts

than the examination made at the patent office, as shown in a study by the United States Federal Trade Commission on drug entry and patent expiration (*25*).

Conclusions

Patents have become a key factor in the R&D process in pharmaceuticals. Although, in certain contexts, they provide the incentives to develop new pharmaceutical products from which society may benefit, by their very nature they limit the diffusion of the innovations that they are intended to promote. When the innovation process is cumulative, strong protection for the first-generation producer limits the scope of second-generation producers, and slows down follow-on innovation.

Patents often establish barriers to entry that are unjustified in terms of the technical contribution effectively made. Low standards of patentability have allowed a significant expansion of patent coverage. Strategic patenting diverts resources into litigation and restrains legitimate competition. While this is taking place in both developed and developing countries alike, it is particularly worrying in the latter since competition laws are in many cases non-existent or poorly implemented, and domestic firms are generally too small to bear the costs and risks of litigation. Developing countries have struggled in the past few years to confirm their rights to use the flexibilities allowed by the Agreement on Trade-related Aspects of Intellectual Property Rights (TRIPS), particularly in relation to parallel imports and compulsory licences.[a] Without abandoning these efforts, they should pay more attention to the way in which patents are examined and granted, in order to avoid abuses and the negative effects on access to medicines that patents on noninventive developments entail. ■

Conflicts of interest: none declared.

Résumé

Propriété intellectuelle - Le rôle des brevets dans la R & D en pharmacie

Le secteur privé, comme le secteur publique, contribuent aux activités de recherche et développement (R & D) dans le domaine pharmaceutique. Le secteur public est à l'origine de la découverte d'un grand nombre de nouveaux médicaments. Le secteur privé, qui axe ses efforts sur le développement, dépend fortement des brevets. Bien que ceux-ci soient supposés récompenser de véritables inventions, le laxisme des lois sur la brevetabilité et les défauts de procédure permettent d'obtenir la protection d'une multitude de progrès mineurs. Ces brevets, quoique faibles et éventuellement invalides dans de nombreux cas, sont utilisés pour restreindre la concurrence et retarder l'entrée en compétition des génériques. Il convient que les pays en développement conçoivent et mettent en œuvre leur législation sur les brevets de manière à prévenir la prise de brevets stratégique et à promouvoir la concurrence et l'accès aux médicaments.

Resumen

Propiedad de los conocimientos - Función de las patentes en la I+D farmacéutica

Tanto el sector público como el sector privado contribuyen a la investigación y el desarrollo (I+D) de preparaciones farmacéuticas. Muchos de los descubrimientos de medicamentos nuevos tienen lugar en el sector público. El sector privado, que se centra en el desarrollo, depende en gran medida de las patentes. Aunque se supone que éstas recompensan auténticas invenciones, la laxitud de las normas acerca de la patentabilidad y los fallos de los procedimientos permiten obtener protección para innumerables desarrollos de poca importancia. Estas patentes, aunque poco consistentes y posiblemente carentes de validez en muchos casos, se usan para restringir la competencia y retrasar la introducción de medicamentos genéricos. Los países en desarrollo deben diseñar y aplicar sus leyes en la materia de manera que prevengan las patentes estratégicas y promuevan la competencia y el acceso a los medicamentos.

ملخص

امتلاك المعارف: دور براءات الاختراع في بحوث وتطوير المستحضرات الدوائية

الملخص: يساهم القطاعان العام والخاص في بحوث وتطوير المستحضرات الدوائية. أما القطاع العام فيبتكر العديد من الأدوية الجديدة. وأما القطاع الخاص، الذي يركز اهتمامه على التطوير، فيعتمد اعتماداً كبيراً على براءات الاختراع. وبالرغم من أن المفترض ألا تُمنح البراءات إلا للاختراعات الحقيقية، إلا أن القواعد غير المحكمة المتعلقة بمنح البراءات، وأوجه قصور الإجراءات، يتيحان التمتع بالحماية التي توفرها براءات الاختراع إثر عمليات تطوير بسيطة. وبالرغم من ضعف هذه البراءات واحتمال عدم صلاحيتها في العديد من الحالات، إلا أنها تستخدم لتقليص فرص التنافس ولتأخير دخول الأدوية الجنيسة حلقة المنافسة. ومن ثَـمَّ، ينبغي على البلدان النامية إعداد وتنفيذ قوانينها الخاصة المتعلقة بمنح براءات الاختراع، لمنع عمليات منح للبراءات على أساس استراتيجي ولتعزيز التنافس وفرص الحصول على الأدوية.

[a] See World Health Assembly Resolution WHA56.27 (2003) which recommends Member States "to use to the full the flexibilities" contained in the TRIPS Agreement.

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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. ■

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