Building local research and development capacity for the prevention and cure of neglected diseases: the case of India

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Abstract This paper examines the proposal to build research and development (R&D) capabilities for dealing with neglected infectious and tropical diseases in countries where they are endemic, as a potentially cost- and time-effective way to fill the gap between the supply of and need for new medicines. With reference to the situation in India, we consider the competencies and incentives needed by companies so that their strategy can be shifted from reverse engineering of existing products to investment in R&D for new products. This requires complex reforms, of which the intellectual property rights agreement is only one. We also consider whether Indian companies capable of conducting research and development are likely to target neglected diseases. Patterns of patenting and of R&D, together with evidence from interviews we have conducted, suggest that Indian companies, like multinational corporations, are likely to target global diseases because of the prospect of much greater returns. Further studies are required on how Indian companies would respond to push and pull incentives originally designed to persuade multinational corporations to do more R&D on neglected diseases.

Keywords Orphan drug production; Drugs, Investigational/supply and distribution; Investments; Research; Motivation; Patents; Drug costs; Drug industry; Developing countries; India (*source: MeSH*).

Mots clés Médicament orphelin; Médicament phase recherche/ressources et distribution; Investissement; Recherche; Motivation; Coût médicament; Brevet; Industrie pharmaceutique; Pays en développement; Inde (*source: INSERM*).

Palabras clave Producción de medicamentos sin interés comercial; Drogas en investigación/provisión y distribución; Inversiones; Investigación; Motivación; Patentes; Costos en drogas; Industria farmacéutica; Países en desarrollo; India (*fuente: BIREME*).

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Introduction

Health and economic development are positively linked, and external investment is needed to break the vicious cycle of poor health and poverty that afflicts the less developed countries. The disease burden per person in these countries, measured in disability-adjusted life years, is twice that in the established market economies. Furthermore, over 40% of the healthy years lost in the less developed countries are attributable to communicable, maternal, and perinatal diseases, many of which never existed or have been all but eradicated in the established market economies (*1*).

The prevention and cure of these neglected diseases have received inadequate attention from global public health and research institutions and from private industry. In 1992, for example, only US$ 2.4 billion were dedicated to these diseases globally, approximately 4% of the total invested in health care (*2*). It has been estimated that the average cost of research and development (R&D) for new products is between US$ 300 and 600 million, and that it takes between 10 and 12 years to get from laboratory to market, although these figures vary with the therapeutic category (*3–5*). Because, in financial terms, the expected markets associated with malaria, tuberculosis, and less well-known diseases such as African trypanosomiasis and schistosomiasis are small, industry does not make them a priority, despite the significant need for new products (*6–8*).

Debate on how to tackle the lack of effective, affordable and accessible products for neglected diseases tends to focus on the following possible approaches. First, combining push (cost-reducing) and pull (market-enhancing) incentives with a view to encouraging private industry to invest more in these

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diseases. Second, establishing more partnerships that pool public capital with private experience in order to target specific diseases on the basis of early progress, which still has to be validated, of disease-focused public–private initiatives, such as the Medicines for Malaria Venture and the International AIDS Vaccine Initiative.

A third approach that warrants consideration in conjunction with the previous two involves building R&D capabilities to focus on new treatments for neglected diseases in countries such as Argentina, Brazil, and India, where emerging pharmaceutical industries and neglected diseases both exist. Local companies in endemic regions might have a greater incentive and a comparative advantage over multinational corporations in carrying out cost-effective research in this field. Economic arguments and empirical studies suggest that there are sizeable challenges to the development of innovative R&D capabilities in respect of neglected diseases. We use the case of India to investigate some of these challenges.

The Indian pharmaceutical industry

Efforts to build R&D capabilities in the developing world could focus initially on countries that already have pharmaceutical expertise and some innovative capabilities. In 1992 it was considered that Argentina, Brazil, China, India, Mexico, and the Republic of Korea met these criteria (*9*). The case of India is developed here.

In many ways, past Indian governments' policies which were geared to develop a self-reliant pharmaceutical industry have succeeded. In 1970, at the time of the introduction of the first policies, the Indian pharmaceutical industry was dominated by foreign subsidiaries of multinational corporations. Only 2 of the 10 pharmaceutical firms with the largest retail sales were Indian. Much of the country's pharmaceutical consumption was met by imports (*10*, *11*).

Steps taken in 1970 and subsequently to promote a domestic industry included: first, the passing of the Indian Patent Act, which eliminated all product patent protection, reduced the period of validity of process patents from 20 to 7 years, and allowed the introduction of automatic licensing; second, the imposition of import restrictions on drug formulations and the introduction of high import taxes on critical inputs; and third, the introduction of price controls. See references *10, 12,* and *13* for an empirical analysis of the coevolution of government industrial policy and the development of the Indian pharmaceutical industry since the 1970s and the likely impact of changes in the intellectual property (IP) regime on company strategies and performance.

Public investment

Significant public investment went into the building of pharmaceutical, chemical, and biotechnology manufacturing facilities such as Indian Drugs and Pharmaceuticals Ltd and Hindustan Antibiotics Ltd. Scientists and engineers were trained and public research institutions, universities, and laboratory networks were created, among them the Council of Scientific and Industrial Research and the Indian Council of Medical Research.

By 1999 between 8000 and 20 000 mostly small, Indian-owned companies, employing more than 2.86 million people, dominated the industry (*14*). Between 1965 and 1997 the value of formulation production and bulk drug production increased by factors of 80 and 145, respectively. Indian-owned firms accounted for more than two-thirds of this output (*13*). Indian export sales have also grown rapidly, although a breakdown by product and destination is needed in order to assess the quality of this achievement.

Strategic plans

To accomplish this rapid development the majority of Indian companies have pursued a reverse engineering strategy, imitating and producing drugs patented in other countries and selling them in India and some international markets. Some 20% of the brands marketed by the 15 leading Indian firms in 1993 were based on new chemical entities covered by European patents (*10*). A further 37% were based on new chemical entities whose patents had expired between 1972 and 1993. It is arguable that stiff price controls, weak IP regimes, and fierce competition have driven companies to seek innovative ways of making products affordable (*15*).

Returns and investments

Profits are currently low and companies tend not to invest in R&D relating to new products. It has been estimated that in 1999 the industry invested 1.8% of sales in research and development (3.5% for the top 10 Indian companies), whereas 15% of sales were invested on these items by parent groups, i.e. multinational corporations. Taking into account the small value of Indian sales and the low prices relative to those of multinational corporations, this percentage suggests that there was little investment in R&D. Formerly, R&D was largely concentrated on process development for known bulk drugs, albeit through novel and innovative process routes. As a consequence, India's R&D forte has been in synthetic organic chemistry and process development. A few new drugs have emerged from Indian R&D involving the use of conventional screening techniques, but none have been blockbusters (*11*).

Creating an environment for R&D

If Indian companies are to advance to the discovery and testing of new drugs it would seem necessary to bring about a change in incentives and sizeable investments in new technologies, skills, and capabilities (*16*). A new regime of industry policies is called for.

In particular, the strategic trajectories of Indian companies described above are often linked to weak IP regimes. Under the trade-related aspects of intellectual property rights (TRIPS) agreement, product and process patents are to be protected for 20 years from the date of filing of patent applications. The required national patent law amendments for pharmaceutical inventions can be delayed until January 2005 in developing countries and until January 2006 in the least developed countries (*17*). As developing countries move to implement the patent laws under the TRIPS agreement, two key questions arising from the global IP debates become important. First, will strengthening IP rights lead to more R&D by either domestic or foreign subsidiaries based in less developed countries? Second, will the long-term benefits of these new investments outweigh the predicted costs of price increases, the loss of businesses and jobs, and a decline in trade balances? See reference *10* for a thorough study of the static and dynamic effects of strengthening the IP regime in India, and references *17–19* for analyses of the links between IP and price. For present purposes we focus on the first question.

Intellectual property and R&D

The global pharmaceutical industry promotes strong IP protection as a necessary, although inadequate, driver of pharmaceutical innovation. The costs and time involved in new product R&D are much greater than those required for making copies. The International Federation of Pharmaceutical Manufacturers Associations posits that the less developed countries stand to benefit from a stronger IP regime. This, it is expected, would make the regions concerned more attractive for foreign direct investment and technology transfer. Furthermore, the less developed countries' local industries would be motivated to invest in R&D activities, either on their own or in partnership with international companies (*12*, *20*). India's sizeable pool of low-cost and technically skilled scientists makes it potentially attractive in this connection.

There is evidence of a strong negative correlation between weak IP regimes and foreign direct investment on the one hand and technology transfer on the other (*21*, *22*). However, the importance of cost among the factors driving decisions on R&D made by multinational corporations has been questioned (*13*). Moreover, unlike the production and distribution of drugs, research centres tend not to migrate to other parts of the world (*9*). It is therefore unclear whether the strengthening of IP regimes would motivate new foreign direct investment in developing regions.

Historical accounts of the pharmaceutical industries in Europe, Japan, and the USA suggest that incentives to innovate, including strong product patent protection, confer an advantage to innovators but are not enough to promote innovation in contexts where innovative capabilities are low or absent (*16*). India's leading companies — those aspiring to participate in the global pharmaceutical industry beyond 2005 and to implement TRIPS — are already working to increase the total share of investments spent on product R&D and to search for new molecules rather than conducting imitative process development research (*13*, *15*). It is unclear how many other companies are or will be able to follow their lead.

Beyond intellectual property: other obstacles to capacity building

If Indian companies are to enter the field of drug discovery a number of requirements have to be met, including legislation that encourages innovation, encompassing tax, intellectual property, technology transfer, and price rules; a broad, well-resourced, public and private research base; adequate pools of skilled scientists, technicians, engineers, and managers; public and private venture finance to support entrepreneurial projects based on chemical and biological science (*23*).

India has taken steps in recent years to address all of these issues, although much remains to be done. By themselves, IP reforms cannot be expected to drive a critical mass of companies into R&D on new drugs (*16*, *24*). In an attempt to improve the rewards for R&D, the Drug Policy Control Order stipulated that innovative drugs and processes developed and produced in India would be exempt from price control for 5, or, in the case of new drugs, 10 years (*13*). Guidelines on how companies could qualify for a 10-year tax holiday on income arising from R&D were also made public in May 2000 (*25*).

Research capabilities

Successful drug discovery depends on strong life science and chemistry research bases and effective technology transfer policies to facilitate commercialization. In India, public research institutions and universities still require substantive inflows of cash to modernize existing facilities and to catch up with technological advances in traditional chemistry as well as in genomics and biotechnology.

The brain drain

India and China are among the countries with the largest numbers of science and engineering students. In this respect they ranked third and fourth, respectively, behind Russia and the USA in 1992 (*26*). Many of the Indian and Chinese students train in the USA or other industrialized countries and then stay abroad because of good facilities, easier links with colleagues, and better rewards for their efforts in the established market economies (*27*). The development of a strong R&D base requires these students to be given incentives to return to or stay in their home countries.

The need for extra resources

Few companies are in a position to self-finance R&D. Consequently, public and private resources are needed. In India, public funds for R&D, under the control of the Department of Science and Technology, are in place but are considered inadequate in relation to present and projected demands for high-risk finance. Proposals to improve the operating conditions for venture capital funds and the financing of targeted drug discovery are under consideration but effective action has thus far been hampered by political disputes (*13*). A proposal to set up a US$ 33 million-seed-fund to promote domestic pharmaceutical R&D was accepted in February 2000 and approved by the Finance Minister in September 2000. All the money had to be spent by March 2001 (*25*).

Deficiencies in infrastructure

Getting a product to market involves far more than just incentives and competencies to do discovery research. The Pharmaceutical Research and Development Committee of the Council of Scientific and Industrial Research (*11*) has completed a report detailing the strengths and weakness of the Indian infrastructure and identifying where new investments are needed in order to bring the clinical trial research and approval phases up to internationally competitive standards. The requirements include reforms to allow animal importation and testing, investments in clinical trial centres conforming to good clinical practice, in vitro testing facilities, and the training of clinical pharmacologists, IP managers, and staff for the Indian drug approval agency.

Assuming that these resources and incentives can and will be made available — a long-term process at best — the critical question from the global health standpoint is whether Indian companies are likely to channel any innovative capabilities towards developing new products for neglected diseases.

Limited prospects for research into neglected diseases

It has been suggested that, under new IP regimes, local companies may be motivated to increase investment in research on neglected diseases (*13*, *28*). This possibility has been put forward on the basis that, with the potential to discover and develop drugs at a fraction of the costs incurred by global players, local companies can make a neglected-disease strategy profitable despite the low purchasing power of the patients. It is argued that volume sales of low-priced products can be economically viable if the R&D costs are sufficiently low.

This proposition seems weak. In addition to the required investments, companies need to move along a steep and rapidly evolving learning curve in order to achieve the desired cost levels. Most Indian companies have done little or no extensive R&D of the type required to discover, develop, and market a new product. Moreover, even if companies were capable of achieving such low costs, money-making opportunities would still be much greater for rapidly growing global diseases than for neglected diseases, notwithstanding significant differences in cost structure between these two categories.

Where does the R&D focus lie?

In interviews, executives of India's leading companies revealed a global focus (*12*). These companies seek to exploit their traditional experience and cost advantages in the generic drugs market or in improving the drug profile by modifying existing drugs or discovering new classes of molecules for well-understood diseases (*29*). Those looking to increase their in-house R&D facilities emphasize the importance of major diseases in industrialized countries, e.g. cancer and diabetes. In the USA, for example, marketing approval by the Food and Drug Administration is quick and even a moderately important discovery is likely to be significantly profitable (*13*). As of 1999, only 16% of R&D expenditure in India was targeted on tropical diseases or developing-country markets, and about half was focused on developing more suitable products for diseases of global incidence (*17*).

Local solutions to local diseases?

The Indian Government has given priority to investment in new drug development for diseases of relevance to the Indian population. Among these diseases are tuberculosis, malaria, and leishmaniasis. Without explicit targeted incentives, however, such investment is unlikely to take place. The Pharmaceutical Research and Development Committee has proposed the establishment of a support fund through a tax on formulations sold in India (*13*). This would help to fund research in areas of combined high cost and low return, e.g. neglected diseases. It is unclear who would decide how to allocate the money. Of particular importance is the question of whether the estimated US$ 22 million generated annually by such a scheme would serve as an adequate incentive. Another way of encouraging greater interest in priority disease areas might be to adopt the Government's tax-holiday proposal and focus on innovations in these areas.

Conclusions

To break the vicious cycle of disease and underdevelopment, significant investments should be made to improve the health of populations in the less developed countries. The treatment and eradication of neglected diseases should be among the top priorities, others being nutrition, sanitation, and education. The key question arises of how scarce global resources can be allocated in order to achieve this.

Potentially large economic and social benefits could be gained by enabling private companies and research institutions in endemic regions to contribute to R&D work on new treatments. Furthermore, research facilities based in these regions may be comparatively well placed to achieve quick solutions. This is because the practice of health research relies heavily on close contact with other parts of the health sector, on the local epidemiological environment, and on the clinical, behavioural, and social sciences that are tied to both national and global frameworks (*27*).

However, creating conditions for innovative and cost-effective drug discovery and development and for a critical mass of companies focused on R&D requires significant investment in facilities, institutions, and skill building. This paper has focused on India, but other countries with emerging industries face many of the same challenges in their own institutional contexts. The Indian companies most likely to survive the changes in patent laws are those that can exploit traditional strengths in areas of generic drug production and innovative process development, and find markets in industrialized countries. Driven by the need to earn profits, companies wishing to succeed in the field of drug discovery are likely to target growing and potentially profitable global disease areas.

An important question arises as to whether the types of push and pull incentives that some European countries and the USA are considering, in relation to the R&D priorities of multinational corporations, would work in India. If one or many global purchase funds were set up — this being the leading pull option currently under consideration — Indian companies could theoretically compete for a share. However, to be most effective, incentives should probably take explicit account of the distinct cost structures, skills, and strategic capabilities of companies in the less developed countries, just as different policies are needed to encourage the participation of small, often loss-making biotechnology companies, as opposed to multinational corporations. How global incentive packages should be designed and executed are topics for important research in the future. In the end, no single country should or can afford to bear the burden of building incentives and carrying out research for neglected diseases. ■

Conflicts of interest: none declared.

Résumé

Création de capacités de recherche et développement locales pour la prévention et le traitement des maladies négligées : cas de l'Inde

L'objet du présent article est d'examiner la proposition de création de capacités de recherche et développement (R&D), dans le but de s'attaquer aux maladies infectieuses et tropicales négligées dans les pays où elles sévissent sur le mode endémique, et de disposer d'un moyen potentiellement efficace en temps et en coût pour combler l'écart entre la fourniture et le besoin en nouveaux médicaments. Considérant la situation en Inde, nous tenons compte des compétences et des incitations nécessaires pour que les firmes puissent modifier leur stratégie et passer de l'ingénierie inverse des produits existants à l'investissement dans la R&D de nouveaux produits. Des réformes complexes s'imposent, les accords sur les droits de propriété intellectuelle n'étant que l'une d'entre elles. Nous examinons également la question de savoir si les firmes indiennes capables de conduire la recherche et développement sont susceptibles de s'intéresser aux maladies négligées. Les modalités du droit des brevets et de la recherche et développement, ainsi que les indications tirées des entretiens réalisés donnent à penser que les firmes indiennes, comme les firmes multinationales, risquent de s'intéresser aux maladies mondiales, en raison des perspectives de rentabilité bien supérieure. Des études complémentaires sont nécessaires pour connaître la manière dont les firmes indiennes répondraient aux mesures incitatives/dissuasives (*push and pull strategy*) conçues à l'origine pour convaincre les firmes multinationales d'effectuer plus de R&D sur les maladies négligées.

Resumen

Creación de capacidad local de investigación y desarrollo para la prevención y el tratamiento de enfermedades desatendidas: el caso de la India

En este artículo se examina la propuesta de crear medios de investigación y desarrollo (I+D) para afrontar enfermedades infecciosas y tropicales desatendidas en países en los que son endémicas, como opción potencialmente costoeficaz y cronoeficaz para colmar la brecha existente entre el suministro y la necesidad de nuevos medicamentos. En relación con la situación en la India, analizamos las competencias y los incentivos que necesitan las compañías para desplazar su estrategia de la retroingeniería de los productos existentes a la inversión en I+D de nuevos productos. Ello requiere reformas complejas, entre las cuales el Acuerdo sobre los Aspectos de los Derechos de Propiedad Intelectual es sólo un ejemplo. Consideramos asimismo la probabilidad de que las compañías indias capaces de llevar a cabo actividades de investigación y desarrollo aborden algunas de esas enfermedades desatendidas. Las modalidades de concesión de patentes y de I+D, unidas a la evidencia aportada por las entrevistas que hemos realizado, parecen indicar que las compañías indias, al

igual que las empresas multinacionales, estarían probablemente interesadas en abordar enfermedades mundiales dadas las perspectivas de unos beneficios mucho mayores. Se requieren nuevos estudios para determinar cómo responderían las compañías indias a los incentivos impulsores y atractores concebidos originalmente para persuadir a las empresas multinacionales a emprender más actividades de I+D relacionadas con enfermedades desatendidas.

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