

Bio-business in brief: a case for new drugs at generic prices from India

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The current drug discovery paradigm in the West is constrained in what it can do, primarily due to the funding model. Here we envisage a hypothetical non-governmental, non-profit organization called the Centre for Affordable Medicine. By sourcing innovation from a network of academic and corporate partners, and working primarily in India, it could lower the cost of innovation. Funding could be from a variety of players that expect a social, not financial, return. The drugs thus developed could be licensed out to a limited number of generic pharma companies, and thus be available at generic prices immediately.

Keywords: Affordable medicine, drug discovery, funding model, generic and innovative drugs.

It is well known that big pharma is in trouble, with weak drug discovery pipelines. What is discussed less often is that about 70% of the drugs approved in the United States (US) are no better than what is already available in the market^{1,2}. Also, only 40% of the drugs in development are abandoned for reasons of safety or efficacy, with 60% killed for financial or other reasons³. Another issue that has attracted attention in the last few years is that very few drugs are developed for diseases that primarily affect those with an inability to pay⁴. Separately, it is also known that most of 'chemical space' has not been explored and therefore potentially useful chemical structures have not been exploited⁵. Thus drug discovery has often been conservative in terms of what could be achieved scientifically and has probably not achieved its full potential in terms of medical impact.

The funding paradigm

Why has this situation arisen? It is primarily due to the pressures resulting from the current mode of financing the drug discovery process. A young company doing drug discovery needs venture capital to get anywhere. Over time, it has to raise tens or hundreds of millions of dollars, and the institutes putting in that kind of money have certain expectations of large returns. Likewise, a large pharma company investing in drug discovery does so with an eye on Wall Street's expectations of double-digit growth. Either way, drug discovery takes place primarily with an eye on financial returns. This then leads to 'rein-

venting' drugs that are doing well commercially, to the development of drugs for chronic diseases in particular, to the neglect of infectious diseases, to high drug prices in general, and also to other unethical practices⁶.

Is there an alternative to this funding paradigm? There have been suggestions for a radical overhaul of the drug discovery process, involving a separation of the costs of R&D from those of manufacture, and suggestions for where funding for the former might come from^{2,7}. There have also been a variety of suggestions, especially in the area of neglected diseases such as: (a) novel incentives, like advance price commitments and vouchers for a speedy review of new drug applications in exchange for the development of drugs against neglected diseases⁸, and (b) open source, that is, an 'open' source of contributors to the drug discovery project, be they from private or public institutions⁹. In terms of the steps already taken, there have been two kinds of efforts, both for neglected diseases. (i) There are about two dozen public-private partnerships (PPPs)⁹. (ii) There have also been a few non-profit organizations, such as the Institute for OneWorld Health (iOWH), that are trying alternative ways of bringing drugs to the market. In both cases there has been medical success. For the Meningitis Vaccine Project, a PPP, a Meningitis A vaccine has been developed and administered to 12 million people (95% of the focus population) in Western Africa. iOWH has brought to market the drug paromomycin to treat visceral leishmaniasis. However, in both cases, the efforts are of relatively recent origin and the financial sustainability of such endeavours is yet to be determined.

A novel organization

Here we imagine an institution that produces new drugs – for any disease – at the price of generics. Let us name the

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proposed organization as Centre for Affordable Medicine (CAM). Thus, the mission statement of CAM may be as given in Box 1. Although drugs are only one aspect of healthcare, and there is need of innovation in other areas such as diagnostics, devices, protocols and so on, which CAM could also work on, our discussion primarily concerns drugs.

Let us also envisage the goals of CAM (Box 2). Given the mission statement, it follows that producing low-cost drugs and enabling ready access to them is a key goal. It also follows from this that costs need to be kept down at every step, with the qualifier that scientific and other ethics will not be compromised. Given the location in India, an additional goal could be to view the process as contributing to training of much needed R&D manpower. If the skills of scientists involved with these projects can also be leveraged for other training purposes, that would be a useful contribution to spreading these skill sets around the world. Finally, in the spirit of enabling other efforts, knowledge gained will be put into the public domain either as research publications or in other useful formats that are easy to access.

We need to consider the conditions under which it would be possible to create CAM, where the discovery end looks like a biotech company and the sales end like a generic company. What legal structure should CAM have, and what scientific and financial strategies must be pursued to fulfil its mission? Also, what other guiding principles need to be decided upfront, such as those concerning relationships with existing companies, ownership of intellectual property, and future licensing and pricing

Box 1. Mission statement of the Centre for Affordable Medicine (CAM)

To discover and develop effective drugs and other healthcare products and processes that are affordable by and accessible to most people.

Box 2. Goals of CAM

1. To discover and develop drugs that are immediately available at prices typical of long-standing small-molecule generics.
2. To make every effort to reduce costs at every step of the process, without compromising on the quality of the science or ethics.
3. To enable the developed molecules to be widely available.
4. To view each step of the drug development process as contributing to training the much-needed drug discovery and development manpower in India. Also, to expand this training where feasible.
5. To work on non-drug healthcare products and processes.
6. To contribute knowledge to the public domain in formats that others can build upon.

strategies? Thus, the proposed initiative first and foremost needs discussion of such matters, followed by the need for a map of the operational paradigm. The latter should receive a variety of inputs, such as from: (i) those experienced in drug discovery, either within the standard paradigm or alternatives if they exist; (ii) credible professionals who have ideas of how to improve the process, and, (iii) those who have been working outside the US and Europe and have already found ways to be more efficient or to reduce costs in other ways. Some of the questions that need answering include the following: Which areas should be the focus for the drug discovery efforts? Can one identify projects that have promise, but that have been shelved due to the compulsions of the balance sheet or some other reason? How might one identify which aspects of the programme could take place in 'open source'⁹ or 'distributed' fashion¹⁰? Should there be an attempt to make traditional medicine a starting point for some projects? How many projects should be handled at a time?

Funding

One cannot discuss drug discovery without first considering the issue of funding. Even the most cost-effective programme will – at the very least – require tens of millions of dollars before there are any revenues. At the outset we outlined the problems that arise when drug discovery takes place in a mainstream for-profit drug company. Although such companies are also involved in the PPPs that are tackling neglected diseases, their contributions are small, as discussed below. In practice, therefore, there are potentially three sources of significant funds: philanthropic organizations, individual governments and multilateral agencies (Box 3).

Philanthropic organizations

The Bill and Melinda Gates Foundation, in particular, has been a strong supporter of the PPPs. As of 2006, it had provided almost US\$ 1 billion of the US\$ 1.15 billion spent by foundations on these partnerships⁹, in contrast to US\$ 36 million by for-profit entities. Although its usual 'Grand Challenges' award is up to US\$ 1 million (grandchallenges@sci.scientific-direct.net), it has awarded US\$ 200 million to iOWH (www.f1000scientist.com/article/display/57891/). Furthermore, other billionaires are also being urged to commit significant portions of their fortunes to philanthropy (http://news.yahoo.com/s/ynews/20100616/bs_ynews/ynews_bs2652), and it is possible that some of this could be channelled towards drug discovery.

National governments

Governments have made larger contributions (US\$ 244 million) to the PPPs than for-profit companies. Also, a

Box 3. Possible sources of funding

Funder	Illustrative relevant actions to date	Reference
1 Foreign philanthropy Bill and Melinda Gates Foundation	Multiple efforts, including more than US\$ 1 billion for drug development for neglected diseases	9
2 Multilateral organizations or international government-level collaborations UNICEF, WHO	Assisted India manufacture penicillin for the first time in the 1950s	13
Wellcome Trust–DBT	£45 million partnership to spur affordable healthcare. Funding available to any kind of organization working in India	http://www.wellcome.ac.uk/News/Media-office/Press-releases/2010/WTX060350.htm
3 National governments Government of Oman	Shantha Biotechnic's hepatitis B vaccine	12
4 Private companies Several companies	Participation in public–private product development partnerships	14

large portion of drug discovery of the most efficacious drugs, and also the best-selling drugs, has already been funded by the US Government¹¹. An example closer to home is that of the Government of Oman that invested in Shantha Biotechnic's early efforts at bringing out a hepatitis B vaccine¹². Since the proposed initiative will not focus solely on neglected diseases, the more immediate benefit to society is apparent and should not be a difficult proposition to sell. There have also been recent moves by the Governments of the US (National Center for Advancing Translational Sciences) and of India (Council for Scientific and Industrial Research's (CSIR's) Open Source Drug Discovery initiative and the proposed new drug discovery institute, and the Translational Health Science and Technology Institute) to set up organizations for drug discovery, an admission that more drug discovery has to be done in non-profit mode.

Multilateral agencies

Historically, organizations of the United Nations (UN) in particular, helped develop scientific and technological programmes in developing countries. This included UNICEF assisting India manufacture penicillin for the first time, in the 1950s (ref. 13). In due course this led to the strong generic drugs industry in the country. The large-scale export of generic drugs from India to other countries has led Medicines Sans Frontiers to refer to India as the 'Pharmacy of the developing world'. Although India's large generics industry does not need such assistance today, CAM may require such assistance, at

least initially. Should original drugs join the generics on the shelf, the entire world will benefit.

Private companies

Although there are several cases of the involvement of private companies in the product development partnerships¹⁴, as mentioned above, the contributions have been relatively small.

As drugs start reaching the market, part of the revenue should return to CAM. A drug selling to a large number of people will bring in enough revenue even at generic pricing to make a significant contribution to any corpus/endowment. Indian companies that have sold generics in developed countries have seen huge growth in their revenue¹⁵. One can imagine a similar story for new drugs. Therefore, even within the framework of generic pricing, one can anticipate differential pricing in different markets, and if a fixed percentage of sales is fed back into the corpus, it should sustain the future efforts of CAM.

Aside from funding per se, one can conceive of various types of partnerships that involve in-kind contributions:

(a) Scientists who identify with the mission of CAM, and for whom the scientific challenges of the drug discovery programme make it worthwhile to collaborate. The Myelin Repair Foundation in the US has used this strategy (www.f1000scientist.com/article/display/57891/).

(b) Companies that wish to share expertise, molecules or facilities for the good publicity that it will engender, or in case it is a pre-requisite for later marketing rights.

(c) Governmental or non-governmental organizations that wish to further the Centre's mission by making expertise or facilities available.

Legal nature of CAM

In terms of the category of organization that will work best, there are perhaps only three possibilities:

(a) A for-profit company, funded differently from most drug discovery companies. We are unaware of any such entity anywhere in the world.

(b) A government institute. There are both pros and cons of doing drug discovery in a public sector institute. On the positive side, a government institute is stably funded allowing larger programmes and long-term planning. The benefits of this cannot be over-emphasized. On the flip side a government institute is governed by rules that may reduce its flexibility either at the start or to enable a change of course midway. In an Indian institute, for instance, there are limited flexibilities on hiring: a non-Indian could not be readily hired, and people of similar seniority and experience usually receive the same pay and perks, irrespective of merit. A governmental programme or institute is also harder to dismantle if it fails to achieve its objectives and could become a perpetual drain on the national exchequer.

(c) A not-for-profit company or a non-profit organization. An organization of this sort is likely to be small and nimble, with considerable freedom in its policies. The lack of stable funding is perhaps the biggest challenge, preventing medium- and long-term planning. Nevertheless, talk of a large and assured budget – as will happen in a government organization – makes us somewhat uneasy. An entrepreneurial outfit is one that has to live by its wits. It has to prove itself before it can attract significant funding and is therefore forced to (i) seek ways to reduce costs at every step; (ii) prove that it has superior strategies, and (iii) hire and retain only those who perform.

Is there a solution? Is it possible, for instance, to have a non-profit organization with adequate and assured funding for 5-year periods, with annual reviews of performance and adequate warning before a programme is closed down? We wish to emphasize the importance of the last. In a country like India both academia and industry are small, and the existence of alternate satisfactory professional opportunities cannot be taken for granted. This aspect must be considered if good people are to be attracted to CAM.

The pipeline

Coming to another level of detail, what would the pipeline look like? For each phase – discovery, development and commercialization – we need to examine who will do what and how each stage will be paid for (Figure 1).

Discovery phase

Leads will be provided by those in sympathy with the mission who have suggestions regarding: (a) potentially useful drugs that have been shelved; (b) promising candidate molecules or potential targets; (c) traditional medicine; (d) combination drugs, or (e) new formulations/drug delivery methods. Work will be carried out in partnership with those (in academia or industry) who believe in the mission. Where required and feasible, work will be outsourced, as is happening in many small, virtual biotech companies in the US today¹⁶. In terms of funding, the drug discovery will be paid for by CAM's starting funds, be they from philanthropic organizations, governments or multilateral agencies. No funder will receive monetary returns from these drugs.

Development phase

Clinical development will be outsourced to clinical trial organizations. As for the discovery phase, funding will be from CAM. In case these are companies that wish both to conduct the clinical trials and also manufacture and sell future drugs, there may be upfront payments at this stage in exchange for more favourable licensing terms later on.

Commercialization

The organization will not seek regulatory clearance or undertake manufacture itself. Bids will be invited from companies that agree to non-exclusive licenses to commercialize the drugs. These companies could get the drugs to market directly or through the government or multilateral agencies. Licensee companies will pay the organization a fixed percentage – around 25% – of sales. The revenues will feed into an endowment to fund future work.

Locating CAM in India

Regardless of how innovative the endeavour is, it will be a challenge to bring out new drugs at generic prices. Crucially, the cost of each step of the process will have to be brought down significantly. With this in mind, we think that India is a good place to locate CAM (Box 4). We are aware that the country has not yet contributed significantly to the Western pharmacopoeia. Nevertheless, Indian companies have been performing different bits of the drug discovery and development puzzle, and whereas the country does not have all the required skill sets along the path of drug discovery¹⁷, it is perhaps on its way to doing so. There are also other reasons why India (or any other country with broadly similar scientific and technological competencies) would be a good location to set up

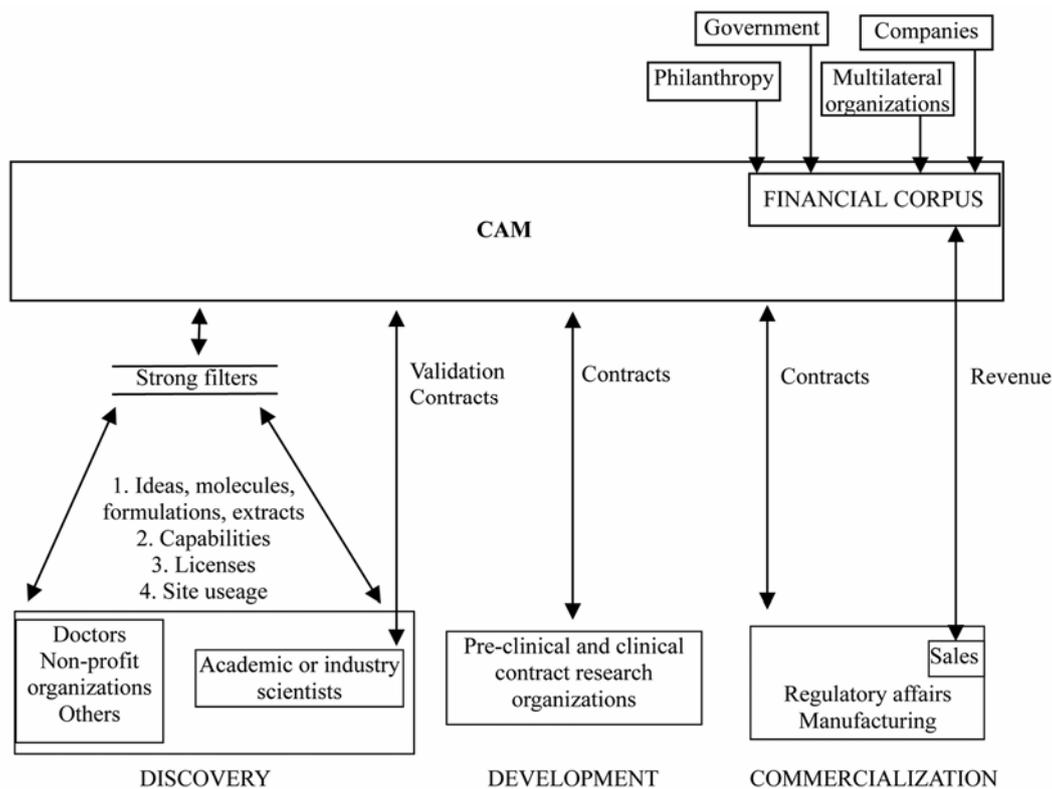


Figure 1. An outline of the Centre for Affordable Medicine (CAM) and its relationship with funding and other organizations.

CAM. (a) In general, technical and scientific skills are fairly high. The country has a large technical and scientific work force and has done well when it has been in ‘mission mode’, that is, where the goal has been well defined. It is one of the few nations that has exploded a nuclear device, has sent shuttles into space and has built an indigenous interceptor missile. Although these mega-projects have been carried out in government institutions, in the private sector too, there is no dearth of technological innovation. A good example is the supercomputer, Eka, produced by a home-grown company, which had a computational capability that was ranked fourth in the world when it debuted in 2007 (<http://www.hindu.com/2007/11/14/stories/2007111453211300.htm>). The roughly Rs 1 lakh car, the Nano, is also the creation of an Indian company. (b) Most customers demand low-cost products. R&D companies in India are discovering that when the inventive process takes place with a different market in mind, interesting things can happen. Ashish Shah of GE Healthcare has talked of how their R&D centre in Bangalore has completely redesigned the ECG machine (Global Engineering and Technology Leadership Summit 2010, Bangalore). From a large bulky machine that is placed in diagnostic centres, they have developed a lightweight, portable machine that travels outside the major cities. In order to make its use more widespread, they have re-engineered various parts of the machine. Illustratively, it works on battery, which makes it more

viable in settings where electricity is unpredictable, and instead of a complex console, it has just three buttons so that less skilled manpower can operate it. The result is an ECG trace for which the patient’s cost has gone down from Rs 175 to only Rs 10. Unsurprisingly, the machine’s sales are rocketing in India, and European markets are also seeing good sales (Oswin Varghese, GE Healthcare, Bangalore, pers. commun.). Thus, when one tries to re-design a process from scratch, many inefficiencies in the established process may be identified. Such examples are contributing to the image of India as a location for ‘frugal engineering’ (http://www.dnaindia.com/money/report_ghosn-back-to-praising-frugal-engg_1130636). Those who are close to the drug discovery process believe that it would cost US\$ 40–70 million to develop a drug from scratch in India, including about US\$ 10–15 million for pre-clinical work (G.S., unpublished). (c) A rich repository of biodiversity and traditional medical knowledge. India has not merely unexplored biodiversity, but also much traditional knowledge, which one could think of tapping into, at least for some projects. What is the best source of such knowledge: a knowledgeable person in the medical community, a scientist who may have worked on flora or fauna and their products, a formal repository of folk knowledge (such as CSIR’s Traditional Knowledge Digital Library) or will it vary with the case? How best should one take this knowledge through a process of scientific validation, including clinical trials? Last

Box 4. Pros and cons of working in India

There are strong reasons for why CAM in India should work out. There are also some uncertainties. We list both sets of issues below.

Pros

- a. Large skill base: In general, there is a large, well-educated population with good technical knowledge.
- b. Low costs: The costs of doing most things are lower than they are in the developed countries. It is believed by those in the know that a first-in-class biologic can be brought up to the stage of clinical testing for US\$ 10 million, and a small molecule for about half of that (Anon., pers. commun.). Clinical trials could cost another US\$ 20–40 million. This contrasts with estimates that a new drug costs US\$ 800 million and upwards (in terms of 2000 dollars) in the US¹⁹.
- c. Ample traditional knowledge: There is much knowledge – tacit or documented – of medicinal plants and their uses. This provides a potentially strong set of leads to begin efforts in drug discovery.
- d. Large number of patients: In all probability, India has every disease in the world, and a large number of patients with each of these diseases. The need, and therefore the potential market, is large. The large number of patients should also ensure volunteers for testing any new drug in development.
- e. Generic pricing works: So far, the health needs of the Indian population have been well met by generic drugs from local drug companies. Furthermore, even with much competition in the generic space, companies have done well. There is therefore much local knowledge on how to ensure affordable pricing while also enabling companies to survive and thrive.

Cons

- a. Small academic and industrial base: The number of scientists in India is small, and thus most science – basic and applied – happens elsewhere. Will there be enough expertise within the country for all the projects deemed important? If knowledge abroad has to be tapped, will it be possible to do so effectively from India?
- b. Absence of sophisticated industrial skill sets: Although there are many well-trained scientists, there is sometimes a lack of ‘ready to go’ industrial professionals. All companies train their scientists on the job, and the pool of such people is increasing. The question is whether there are enough in the country or more have to be brought from abroad for a few years, either in person or as consultants from afar. Would work need to be out-sourced to the US, for instance, and could this be done effectively and without raising costs to an unsustainable level?
- c. Trials in India: It is common knowledge that the Government of India tends to approve only drugs that are already approved in the US or Europe. This then requires that any novel product be put through trials abroad. Any such requirement will significantly raise the cost of the drug. Hopefully the situation will change, and trials of home-grown novel molecules will become a reality in India.

but not least, how does one repatriate the rewards to the holders of the knowledge? If there is a paradigm for satisfactory technology transfer from traditional knowledge holders to companies or other entities interested in drug discovery, this paradigm is not widely known. It has also been argued that such repatriation is unworkable, and regular patent protection may be the best way to handle the issue¹⁸. (d) India has a large population and enormous unmet medical needs. This not only guarantees any company a large market, but also ensures that there are enough patients for clinical trials. However, discussions with a few drug discovery companies in India reveal that it is not straightforward to obtain permission for clinical trials of new molecules in the country (G.S., unpublished). (e) Generic pricing works. Indian companies have a lot of experience in making generic pricing work. Even

in a very competitive market, companies not only survive but often do well. If the R&D costs of developing a new drug have been taken care of, it should not be difficult to find manufacturers who will produce and sell the drug at generic pricing.

Let us therefore try to visualize the drug discovery process as it might happen in India. A few cities – Bangalore, Hyderabad, Pune and Delhi – have clusters of both academic institutions and bio/pharma companies and would be the first choice in terms of locating CAM. Coming to who should head such a programme, there may be an automatic assumption that an Indian has to head it. We do not believe this has to be the case. It may be necessary to import foreign talent for a few years to jump-start the process. On the other hand, someone with good experience in India may have a greater chance of success.

Whatever the legal nature of the organization, it must necessarily be entrepreneurial. It will require extraordinary drive and imagination, along with the risk-taking and proselytizing abilities of an inspired leader. It will also need strong project management skills. The Governing and Advisory bodies will need to be international, and must bring to the table the right scientific and managerial talent and suitable networks along the entire drug discovery pipeline.

Summary

The proposal above discusses the importance of getting away from the steep profit motive required by the financial markets, for drug discovery that results in affordable drugs. We propose a non-profit organization that retains the entrepreneurial nature of a small biotech company, but whose output is as affordable as generic drugs. We go on to propose that such a programme be taken up in India, where drug discovery can perhaps be done at less than 10% of the alleged cost in a developed country. One of the biggest challenges will be to find the funds for an admittedly expensive undertaking. We have outlined how philanthropists, governments, multilateral agencies and perhaps private investors could contribute to prime the pump, with subsequent revenues giving the programme a good chance of self-sustainability. Billions of dollars have been spent unproductively: it is possible that a small fraction of this amount could bring out drugs and other healthcare products and processes that we are all grateful for.

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