

The Cure is Here

Ahmed A. Azad describes the immense opportunities for a research-led pharmaceuticals industry in Bangladesh

Current status of the pharmaceutical industry in Bangladesh: The pharmaceutical industry in Bangladesh has the potential, not only to provide quality drugs at affordable prices, but also to lessen the almost total dependence on the export of manpower and ready made garments for the country's foreign exchange earnings. Although the industry has posted some very impressive figures in recent years, it cannot afford to become complacent. Currently, the total sale of pharmaceutical products in Bangladesh is approximately US\$ 585m, of which 97% (or SD567m worth) comprises of locally produced generic medicines. This substantial saving in foreign exchange could be even more impressive if Bangladesh did not need to import 80% of the active ingredients and precursors.

Jeffery Hamilton

In five years time, domestic demand for pharmaceutical products is projected to increase to, at least, US \$1.88 billion. Now, the question before us is: "Can the industry meet this demand and also maintain, and even improve, its position in the international market?" The answer to this question depends on its ability to correctly (a) assess where it is now; (b) envision where it needs to be in the next 10-12 years; and (c) formulate and adopt the policies and

strategies required to take it there.

The August 6th issue of the Financial express reported that export of medicines from Bangladesh grew 6.21% to US\$ 45.67 million in the fourth quarter of the last financial year, a remarkable turn around from the 16% negative growth witnessed in the preceding three quarters as a result of the global recession. Mr. Abdul Muktedir, the Secretary General of Bangladesh Association of Pharmaceutical Industries (BAPI), attributed this revival to the surge in orders from Western countries and contended that the extent of growth would have been even higher had it not been for the prevalent energy crisis which prevented many factories from achieving optimal production.

In a meeting with the Prime Minister last June, BAPI asserted that the industry is not only capable of meeting the increasing domestic demand but is also well positioned to become a major player in the global market. The PM was further informed that, after meeting local demand, Bangladesh is currently exporting to over 70 countries and that pharmaceuticals could, in fact, become the largest foreign exchange earning sector if the Government removes some legal barriers. A number of recommendations aimed at making the pharmaceutical industry internationally competitive and ensuring the safety and efficacy of all locally produced drugs were placed before the PM.

The main recommendation from BAPI is for the modernization of the existing Drug Administration Authority (=DAA), the industry watchdog which monitors, controls and certifies the production and sale of medicine in Bangladesh. A powerful DAA equipped with state of the art testing facilities and manned by a team of qualified personnel operating within a framework of clear-cut strictly enforceable regulations is urgently needed to ensure that no unsafe or sub-standard medicines ever reach the market. Only then can we avoid a repetition of the recent tragic incident involving production and marketing of toxic paracetamol syrup by a local pharmaceutical company. To this end, BAPI has requested the establishment of an Independent Drug Testing Laboratory and a Clinical Testing Bioequivalence Centre.

BAPI has also requested the government to establish an Active Pharmaceutical Ingredients Industrial Park to minimize the dependence on import of expensive chemical ingredients and thereby lessen the cost of production. The government has reportedly agreed to meet all these demands.

According to a recently released report by PricewaterhouseCoopers (PwC) on the future of the Pharmaceutical industry, the global market for medicines will more than double in value to US\$ 1.3 trillion by 2020. This huge increase will stem from worldwide demands for medicines for an ageing population and for increasing levels of chronic and infectious diseases. Many diseases such as

hypertension and diabetes which, till recently, were largely endemic to the developed countries of the West have now become common in developing countries. With increasing emissions of greenhouse gases and global warming, there is likely to be an increase in waterborne diarrhoeal diseases, infectious diseases such as malaria and tuberculosis and a higher prevalence of respiratory illnesses such as asthma.

So once again the question is, how well-prepared is Bangladesh to meet the challenge of this burgeoning market? We are the largest manufacturer of pharmaceuticals amongst the 45 least developed countries (LDCs) but this isn't saying much since we rank a lowly 13th among the 15 most promising pharmaceuticals manufacturing countries in the developing world. According to PwC, the E7 countries (China, India, Brazil, Russia, Mexico, Indonesia and Turkey) account for roughly 20% of the global pharmaceutical market. Bangladesh is capable of garnering a share of this market if it is prepared to make appropriate and adequate investments in technology and expertise and if the government provides the necessary regulatory support.

As an LDC, Bangladesh currently has an advantage over the E7 countries because of the patent-free regime available to it for the next seven years but after 2016, there is likely to be a sharp decrease in sales unless local manufacturers are prepared to change their product portfolio. In the not too distant future, the global market is likely to be dominated by drugs which are protected by patents and those which require an array of new technologies for their development. Whether Bangladesh can rise to the challenge depends on how quickly she can enhance and mobilize capacity both physical and intellectual) through greatly increased in-house industry investment in research and development (R&D), collaboration between industry and research groups in universities and research institutions and industry funding of research initiatives. Government initiatives such as tax incentives for private sector investment in R&D and abolition of legal barriers mentioned earlier could also help considerably in this regard.

Future international trends and corrective measures:

According to the PwC report, pharmaceutical companies that currently concentrate heavily on a small number of blockbuster drugs for maximum profitability will be adversely affected by a number of market related factors in the near future. In spite of doubling their investment in R&D in recent times, the large multinational companies are facing a serious dearth of new compounds in the pipeline. The main reason for decrease in productivity is operational conservatism and lack of innovation. With new knowledge and technologies, there will be many new opportunities but the pharmaceutical industries will not be able to capitalize on these opportunities unless the R&D productivity improves. The PwC report suggests that in the next decade the

industry must shift its focus more towards research and less in packaging, sales and marketing. The report also suggests that in the future companies will be rewarded more for new therapies rather than “me-too” medicines, and risk sharing with industry and academic partners will become the norm.

The PwC report also emphasizes the importance of adopting new technologies that will drive future R&D. Transformational technological changes in the pharmaceutical sector will shorten the R&D cycle of new products. Knowledge learned from the human genome will open up many new opportunities in the molecular biosciences and provide novel insights into disease-defining molecular targets. The development of new molecular delivery platforms could also speed up the development of new therapeutics. Increasingly, the focus will shift from treatment to prevention in recognition of the cost effectiveness of preventing diseases in healthy populations. The market for preventive vaccines is growing rapidly and is expected to grow to US \$42 billion by 2015. There are currently over 250 new vaccines in clinical development of which a sizable number owe their existence to the availability of genetic engineering technologies (molecular biotechnology). This could be good news for the developing World, where the incidence of infectious diseases is already quite high and might very well become unbearable as a result of climate change unless the new generation vaccines produced in the West are made available to them at affordable prices.

The PwC report also emphasizes the importance of biopharmaceuticals which are organic molecules such as hormones, enzymes and receptors that are produced by the body to regulate physiological processes. Medical biotechnology has made it possible to produce large quantities of highly purified biopharmaceuticals such as insulin that is widely used in Bangladesh. The current market dynamics and future outlook for biopharmaceuticals looks very promising (researchandmarkets.com; Frost & Sullivan, UK, 2009). Although biopharmaceuticals currently account for less than 10% of the total pharmaceutical market, there is every indication that it will increasingly occupy a greater share of the market in the near future. The global market for biopharmaceuticals, which is currently valued at US \$48 billion, has been growing at an annual compound growth rate of 19% since 2004. The biopharmaceuticals segment is expected to continue outperforming the total pharmaceutical sector and could surpass US \$100 billion by 2020.

While there is a dearth of new pharmaceuticals in the pipeline, biotechnology-derived products account for over one third of all new products under development. A very significant proportion of these originate from smaller biotechnology companies that are generating new candidate drugs and

intellectual property (patents) often in collaboration with academic research groups. Besides new subunit and recombinant vaccines, products in the pipeline also include novel drugs aimed at curing complex diseases where conventional pharmaceutical products have been less successful. Regulatory approval rates for biotech products have been much higher than for small molecule candidates and this is driving the growth of the biopharmaceuticals segment in the market. /P>

Advances in enabling technologies that constitute modern biotechnology such as bioinformatics, genomics, proteomics, structural biology and computational chemistry are opening up new horizons for the discovery and development of new classes of biopharmaceuticals, diagnostics and rationally-designed new chemical entities (NCE) that do not exist in nature. It should be noted that most of the new generation biopharmaceuticals and NCEs are being discovered and optimised in biotechnology companies and academic institutions while clinical trials, large-scale production and regulatory processes are being carried out in partnership with more established pharmaceutical companies. This is increasingly the direction in which pharmaceutical R&D, manufacture and commercialisation is moving.

The local pharmaceutical sector needs to adapt to emerging challenges:

At this point in time, the Bangladeshi pharmaceutical industry is doing quite well in meeting domestic demand for common medicines and exporting medicines to both developing and developed countries. Market penetration, especially in the poorer countries, of locally produced medicines is expected to improve because of the high quality and the relatively low cost of manufacture. However, to maintain this market position the pharmaceutical industry in Bangladesh will need to keep pace with new developments and adopt strategies to meet emerging and future challenges.

Most of the medicines being manufactured in Bangladesh are small molecule generics which are copies of mostly "out of patent" medicines originally developed in the West. There are very few of these small molecule drugs in the pipeline, and companies producing them are continually improving their efficacy through chemical modifications and protecting these improved medicines through rolling patents. Manufacturers of generic medicines, especially those in the developing world, will find it increasingly difficult to copy new and improved medicines in future because of intellectual property issues.

Because of the dearth of new candidate drugs in the pipeline, the bigger pharmaceutical companies are increasingly relying on biotech companies for new protein-based biopharmaceuticals for emerging diseases and genetically-

engineered vaccines for disease prevention and control. Biopharmaceuticals and genetically-engineered vaccines are not yet the major focus of most pharmaceutical companies in Bangladesh as the production of these from basic biological ingredients requires a degree of sophistication and R&D infrastructure that is currently not widely available. But this is the very direction in which the local pharmaceutical industry needs to move in order to keep up with international trends and meet the demands for new medicines.

A very small number of local pharmaceutical companies have been “finishing and filling” some imported bulk biopharmaceuticals (bio generics) and vaccines. One company, Incepta Pharmaceuticals, has already started building the expensive infrastructure and expertise required for the production of complex biopharmaceuticals from basic biological ingredients. Some of the other large companies may not be far behind. There is a strong possibility that, in the next two to three years, some biopharmaceuticals and new generation vaccines could be produced locally from basic starting materials. Initially these ingredients would need to be bought or acquired through licensing agreements. With the development of the necessary expertise and facilities, it will become possible to produce even the basic biological ingredients in Bangladesh thus making the process much cheaper and providing additional flexibility in the development of new medicines.

The development of the required scientific and technical (S&T) proficiency will allow Bangladesh, as an LDC, to develop and manufacture bio generics based on biopharmaceuticals that are still under patent protection in most countries. As mentioned earlier, this opportunity is available only till 2016 by which time the local pharmaceutical industry, in partnership with the scientific community and with the support of the government, would hopefully have developed the capacity to discover and develop new medicines based on its own intellectual property.

In recent times the pharmaceutical companies in the West have experienced a serious downturn because of rising R&D and manufacturing costs, and also because of stiff competition from producers of generic medicines especially for markets in developing countries. A number of multinational drug companies are relocating their manufacturing units to emerging economies such as India and China that are S&T proficient and also have relatively low manufacturing costs. Producers of generic medicines in developing countries will become less viable due to lack of access to new medicines in the pipeline because of patent restrictions. So in recent times there have been mergers of convenience between pharmaceutical companies in the West with technologically competent ones in countries such as India which will allow Western companies to lower cost of production and penetrate markets in the developing world, and Indian companies to gain access to new patented drugs and other drugs under

development.

Such mergers could restrict the availability of know how and active ingredients of new and second generation “out of patent” medicines to pharmaceutical companies in less developed countries with low S&T proficiency. This could make essential new medicines less affordable to people in poorer countries that need them most. Thus, the pharmaceutical companies in the developed countries and their partners in rapidly advancing countries would have no financial incentives in discovering and developing orphan drugs or new medicines and vaccines for diseases that mostly affect the populations of poorer nations. The only solution for the poorer developing countries is to improve their own S&T capabilities and devise strategies for developing their own essential medicines that are more affordable and patent-friendly. In this regard, the more technologically advanced pharmaceutical companies in Bangladesh can take the initiative provided effective partnerships can be developed with competent scientific and academic institutions that have complementary expertise and facilities.

The pharmaceutical industry in Bangladesh, or at least some of the more technologically advanced companies, can in fact play an important role in elevating the S&T proficiency in the country. In India and other rapidly advancing countries of the developing world, the governments have taken the lead in the attainment of S&T competency and the academic and research institutions have fallen in step. Technologically advanced new generation pharmaceutical companies have usually come to the party much later but nevertheless have received very generous financial incentives from their own governments. Unfortunately, in Bangladesh, the scenario has been quite the opposite.

Our policy makers, till recently, have been almost indifferent to the role of science and research in national development and there has been very little interaction between academic institutions and the pharmaceutical industry. Our pharmaceutical industry has introduced modern technology and manufacturing practices without any financial incentives from the government. Through partnerships with academic and research institutions, the pharmaceutical companies in Bangladesh could provide badly needed funding for R&D in return for technology transfer.

Case for a research-led pharmaceutical sector in Bangladesh:

The discovery and development of modern medicines is very expensive, long-term and financially risky. For these reasons, development partners and even most policy makers in the developing world (including Bangladesh) feel that technologically demanding R&D should be left to the pharmaceutical and biotech companies in the West and in the rapidly advancing economies, and

developing countries should limit their involvement to offering cheap labor and profitable investment conditions. This regressive attitude will not only thwart the development of scientific proficiency in the developing nations but also ensure that the development agenda is externally driven. This might also mean that poorer developing countries may never get the medicines that they really need and can afford. At the same time, however, the poorer developing countries like Bangladesh need to realize that they cannot afford to compete with multinational pharmaceutical companies on all fronts and will need to find niche areas of existing strength where they can be internationally competitive. They need to focus on only a few health priorities in the initial stages, and overcome deficiencies by pooling human and material resources through coordination and collaboration.

One niche area where Bangladesh could have competitive advantage would be the harnessing of the abundant biodiversity and indigenous knowledge as the basis for the discovery and development of new drugs targeted to meeting the critical health care needs of the country. Bangladesh is fortunate to be endowed with unique and rich flora and fauna particularly in the forested regions of the Sundarbans and the Chittagong Hill Tracts. Bangladesh also has a wealth of knowledge systems in traditional medicines (Ayurveda, Unani, etc.) and numerous local herbal remedies that have been used since time immemorial by the Bengali and minority ethnic communities. This has provided a huge opportunity for research by ethno-botanists and medicinal chemists which has resulted in many research publications. So why has Bangladesh failed to exploit its abundant biodiversity and traditional knowledge to develop and produce new and essential drugs required for its own health care needs and as a vehicle for the economic development of the country?

The simple answer is that the scientific and technical base required for this initiative is grossly inadequate and there is a serious lack of capacity, infrastructure and funds available for research. There is a lot of research activity, and research publications, based on medicinal plants and medicinal chemistry in countries within the region, but hardly any new drugs have come to the market from these efforts. One of the main reasons is that chemists and biologists have not joined forces to tackle the same problem. Also the research is often carried out in the absence of a disease-defining and target-specific biological assay or identification of possible candidate drugs. Often, such research has done more harm than good because of the leakage of valuable intellectual property to the West as the predominant concern of most researchers is publication. Scientists in Bangladesh, even within the same scientific discipline, are more likely to collaborate with research groups in the West rather than among themselves. We have a very poor record of utilizing the diverse and top grade expertise of our own expatriate scientific community but are surprisingly eager to seek expensive advice from foreign experts.

There needs to be a drastic change in our attitude and research culture if biomedical discoveries are to be transformed into products.

In recent times there has been a greater awareness about validation of claims, and stringent requirement for demonstration of efficacy, safety and bioavailability of traditional medicines. However, the discovery and development of new drugs from natural products and traditional knowledge and accumulated experience of the usefulness of indigenous flora and fauna affords many advantages including the shortening of time for pre-clinical studies and clinical trials. Thus, there is great interest in developing modern medicines from traditional ones. This also affords the opportunity to build research capacity at the same time.

The first phase in the development and production of modern medicines from natural products is research leading to the discovery of potential drugs. Such research is already being carried out by small and isolated groups with backgrounds in life sciences and medicinal chemistry. Unfortunately, so far such research has been largely counter-productive: instead of leading to the invention of modern health-care products, it has given birth to a surfeit of impressive research publications. These publications have no doubt benefited the careers of their authors but they could very well have resulted in the loss of valuable intellectual property since such papers were published without first obtaining patent protection.

In the absence of prioritization and coordination, there is often unnecessary duplication and consequently available expertise which is already scarce is spread too thin. Moreover, in the absence of a proper inventory of the nature and extent of the biological resources (natural product libraries and disease-defining biological assays) available within Bangladesh, productivity will fall short of potential. For the first phase of the drug development process, much of the needed expertise and facilities are already available in Bangladesh. What is required, however, is a change in research culture so that researchers who are currently working in isolation can share their knowledge and resources through collaboration on a few priority projects. The importance of protecting the fruits of research through intellectual property patents also needs to be ingrained in our research culture.

The second phase in the development of modern medicines is pre-clinical studies for the validation and optimization of potential drugs to make them into candidate medicines. This phase will also generate valuable intellectual property that needs to be protected. The success of the second phase requires a level of sophistication and a range of expertise and facilities that is currently not largely available in Bangladesh. In one area, however, Bangladesh may already be ahead. Optimization of candidate drugs by structural analysis

requires the availability of relatively large quantities of very pure genetically-engineered protein molecules. It is gratifying that at least one, and perhaps more, of the major pharmaceutical companies in Bangladesh will soon have the capability of large scale production of new recombinant proteins from basic ingredients.

Scientists working in isolated laboratories within Bangladesh could attain the required critical mass and gain access to cutting edge technologies and specialist core facilities through collaboration and the establishment of a research network between potential "centres of excellence" at various academic and research institutions. The National Institute of Biotechnology (NIB) could serve as the national resource centre for major equipment and core facilities. This requires the government to seriously support the proper development and operations of the NIB, a magnificent structure established at great cost to the public exchequer, which currently remains largely an empty shell. Some of the infrastructure and operating costs could come from development partners and the rest through partnership with the local pharmaceutical companies especially those that have developed the technology to take the development process forward.

The third phase in development of modern medicines is clinical trials of candidate drugs and the large-scale production and commercialization of the most efficacious and safe ones. It is generally considered that this would be beyond the independent capability of poor, scientifically-deficient developing countries and would, therefore, need to be carried out in partnership with big pharmaceutical companies since these processes are extremely expensive. However, Bangladesh has some unexpected advantages. The International Centre of Diarrhoeal Diseases Research, Bangladesh (ICDDR, B) and Bangladesh Institute of Research and Rehabilitation in Diabetic Endocrine and Metabolic Disorders (BIRDEM) have extensive experience in clinical trials and clinical research so that the evaluation of safety and efficacy of candidate drugs could be carried out locally in these established sites at a fraction of the cost usually incurred by multinational companies for similar tests. We will not need to rely on foreign companies for large-scale production and commercialization as we have very well established pharmaceutical companies with the required experience, facilities and financial capability. However, if we do need to bring multinationals on board, the intellectual property (patents) obtained during the first and second phases will come in very handy during negotiation. Besides overhauling of the DAA, the government needs to modernize and strengthen the Patent Office. The pharmaceutical industries also need to considerably strengthen their Regulatory Affairs departments. A

number of very senior regulatory affairs experts of Bangladeshi origin currently living abroad could be called upon to provide necessary expertise if required. => the third phase of the drug development process may not be as daunting as expected.

Concluding

remarks:

There are three major areas of activity where the pharmaceutical industry in Bangladesh is likely to make the biggest impact in the near future. It has already made inroads into two of these, biopharmaceuticals and new generation vaccines. The third area involves the discovery and development of modern medicines from the biota and knowledge of traditional remedies. This is the area most likely to pay the highest dividends because of our rich and unique biodiversity and the heritage of traditional knowledge systems. There are also a large number of isolated research groups who are already working in this area. The highest priority would be to encourage collaboration between such groups with complementary expertise, facilities and biological resources.

By developing sensible national priorities, starting from a strong knowledge base, pooling existing natural resources, sharing multi-disciplinary expertise and facilities, employing rational approaches to the discovery and optimization of candidate drugs and by taking advantage of the relatively low cost of labor, it is feasible to establish a research-led drug discovery and development programme in Bangladesh that can be less time consuming and much more cost effective than similar operations carried out by multinational pharmaceutical companies in the West.

Besides the development and manufacture of useful therapeutic products for the domestic and export markets, this initiative would also create jobs for science graduates and technical manpower. A research-led pharmaceutical industry would also raise the level of S&T proficiency in Bangladesh and lead to much needed capacity development in research, with beneficial knock-on effects for many other areas of science. Since scientific and technological proficiency underpins sustainable development, this initiative must be treated as a top priority by the Bangladesh government and should be supported by science academies, multinational science organizations and funding agencies that subscribe to S&T-based sustainable development in the LDCs.