Drug discovery and developments in developing countries: bottlenecks and way forward

V.A. NYIGO* & H.M. MALEBO
National Institute for Medical Research, Traditional Medicine Research Department
P.O.Box 9653 Dar es Salaam, Tanzania

Abstract: Infectious and parasitic diseases continue to threaten the health of million of people throughout the world, with the major burden being in developing countries. Many of the currently available drugs for the treatment of these diseases face setbacks such as insufficient efficacy, increasing loss of effectiveness due to emergence of resistance, high levels of toxicity, inaccessibility and/or high costs. The driving force for drug discovery and development by pharmaceutical firms has been the foreseeable profit from drug sells. Since most infectious diseases prevail in developing countries and the fact that people living in these countries have poor purchasing power, the market for such drugs are unattractive to these firms. Thus, there has been reluctance for the pharmaceutical companies to engage in the development of drugs addressing diseases that mainly affect developing countries. Although a lot of research to discover new effective and cheap drugs is in progress in the disease endemic countries, it is not yet possible to fully develop leads and drug candidates from natural products, hence people in these countries continue to rely on traditional medicines. Poor economies and technological capabilities, lack of human resources and good management in these countries are the major constraints to progress in research and development work for new drugs. This paper discusses these major bottlenecks in drug discovery and development and suggests the way forward.

Key words*:* drug discovery, traditional medicine, infectious diseases, developing countries

Introduction

Infectious and parasitic diseases are major threats to the health of millions of people throughout the world and particularly in the third world countries (Murray *et al.,* 2001). Despite progress made in the basic knowledge of many infectious diseases, many of these have continued to cause significant morbidity and mortality. It is estimated that, infectious diseases cause more than 90% of all morbidities and mortalities occurring in the world with more than 90% of them occurring in developing countries. Many drugs available for treatment of these diseases however, have developed and many are still developing resistance to the present drugs. Chloroquine, for example which was the most cheap and effective antimalarial drug for many years is now obsolete in most malaria endemic countries (WHO, 1996, Peters & Robinson 2000). Alternative effective drugs are expensive and are unaffordable to poor majority of these countries, thus causing malaria to kill many people especially children under five years and pregnant women. There is also a looming threat of the development and wide spreading antimicrobial drug resistance by most of the pathogens. Thus, many treatment agents for infectious and parasitic diseases are becoming ineffective.

New diseases of public health significance like HIV and Ebola have recently emerged and no effective drugs for cure of the diseases have been obtained. Yet many other diseases may probably emerge in a near future. These disappointing health trends call for renewed strategies on treatment and prevention of infectious diseases. One key strategy among many is discovery and development of new efficacious and affordable drugs.

Health needs and opportunities for new drug discovery

Plants have been found to be interesting sources of such drug leads for targeted diseases among many sources and are traced back since antiquity. Historically, plants have provided a source of driving force for novel drug compounds, as plant derived therapeutic agents have made large contributions to human health and well-being. About 119 pure chemical substances extracted from higher plants are used in medicine throughout the world (Farnsworth *et al.,* 1985). Furthermore, in a survey done in community pharmacies in United States revealed that 25% of all prescriptions dispensed from community pharmacies contained active principles, which are from higher plants (Farnsworth & Morris, 1976).

* Correspondence : Vitus Nyigo; E-mail : nyigoo@yahoo.com

Although recent achievements in molecular biology and biotechnology have significantly increased the production of many protein and polypeptide drugs by genetic engineering, most plant-derived chemotherapeutics are not proteins. Plant medicines are secondary metabolites whose production involves complex biosynthetic pathways utilizing multiple enzymes, many of which have yet to be isolated and characterized. Genetic engineering of the plant derived secondary metabolites is currently a challenging and difficult task. Therefore, plants continue to be a definite source of drugs and lead compounds for drug discovery. Most tropical countries that are actually highly burdened by the diseases are a very rich source of such plants and other natural sources which provide a remarkable opportunity for African countries to develop new drugs to curb a multitude of problems.

Despite the need and obvious opportunities developing countries have, there has been no significant development in drug discovery and development except for some few cases of drug leads and drug candidates. Thus, majority of these countries still rely on drugs developed by pharmaceutical firms in the developed countries. However, the driving force for drug discovery and development by these pharmaceutical firms has been the foreseeable profit from drug sells. Since infectious diseases prevail more in developing rather than developed countries, and the fact that people living in the former countries have poor purchasing power, make the market for anti-infective drugs unattractive to the pharmaceutical firms. The firms have therefore been reluctant in investigating and developing new drugs for the diseases that mainly affect developing countries. As a result, very few drugs for tropical diseases are coming into market.

Recent information have revealed that pharmaceutical research and development of new drugs in the period of 25 years (1975-1999), have provided a total of 1,393 new drugs that entered the market and only 16 (0.01%) were for tropical diseases and tuberculosis (Trouiller *et al.,* 2002). This imbalance has a lot of negative effects and a big challenge to third world countries. Ten years ago, the world spent US$30 billion on health research of which less than 10% was spent on 90% of the world's health problems, a disparity known as the "10/90 gap" (GFHR, 2000). Today global spend on health research has more than tripled to about US$106 billion, yet the amount allocated to the research and development for drugs to treat 90% of the global disease burden has risen by only from US$0.3-0.5 billion to around US$3.5 billion, mainly due to contributions from private foundations, governments, and charities (GFHR, 2002).

One of the major reasons for not putting emphasis on investment for tropical diseases by pharmaceutical firms among other thing has been the poor purchasing power of people living in developing countries. Developed countries only are said to offer profitable market incentives for research and development through individual purchasing power and purchasing through government run health insurance programmes. In Europe for instance, these mechanisms cover 70% of drug costs for 80-100% of the population as opposed to 35% in Latin America and less than 8% in Africa (Kanavos, 1999; WHO, 1997). With public spending on drugs at around $239 per head per annum in countries belonging to the Organization for Economic Cooperation and Development, the pharmaceutical industry has a strong incentive to develop drugs for diseases common for this drug market. By contrast, most developing countries spend less than $20 per year per head on all health programmes whereas it is less than $6 in sub-Saharan Africa, including drug expenditures (WHO, 2000). Thus, developing countries have to put deliberate efforts to find solutions to the existing problems that hinder drug discovery and development.

Bottlenecks to drug discovery and development in developing countries

Economic limitation for research and development

Drug discovery and development is a long process and costly endeavour that requires heavy investment in financial and human resources. Many surveys that have been conducted in USA have indicated that drug discovery and development costs have been rising. Although there are no fixed cost estimates, the most recent estimates stands at US$ 802 million (DiMasi, 2003) spread over 12 years or US$ 880 millions distributed over 15 years (Boston

Consulting Group, 2001). Other information sources have indicated that the current costs are around US$ 900 million for a drug to be into market and takes about 12-15 years (Drug Development 2005**).** The suggested probable reasons for the rising in costs for drug discovery and development process are the increased costs of animal testing and clinical trials (Dickson & Gagnon, 2004). Majority of developing countries, especially African countries, have limited annual national budgets that differ insignificantly from the estimated costs of production of one drug. That is, the cost of production of one drug is equivalent to almost 27% of the Tanzanian national budget. (Tanzanian national budget for 2004/2005 was T.Shs 3,347,538million (=US$ 3,347 million)). Worse still, more than one third of the whole budget is loans and grants from donor countries and almost 14% is for public debt payments. Consequently, annual budget for health research is always extremely small. This has devastating effects in terms of research and development financing and therefore drug discovery and development.

Technological incapability

Poor technological capability is another major constraint for third world countries to make progress in research and development of new drugs. Recently, some few countries like India, China, South Korea and South Africa have made considerable technological advancements (Nwaka & Ridley, 2003**)**. However, majority of the developing countries are still technologically incapable and this has a very negative effect on drug discovery and development pipeline.

Early efforts in drug discovery involved screening of natural products derived from plants and microorganisms and testing them for activity in animal models. This technology which is still a major drug discovery tool in majorities of developing countries and most academic and corporate research is a slow and labour intensive process, although it led to a remarkable plethora of medications available at the end of the 20th Century. The current technologies, meanwhile, have complemented the search for natural products by developing families of compounds with potential biological activity hoping that close family members of natural products may show more effective therapeutic power than the original. The production depends on combinatorial chemistry, which uses automated processes to synthesize large numbers of related chemical compounds with a high degree of structural diversity.

Beyond that, advances in molecular biology, genomics, automation and detection, and informatics have shown the way to a new paradigm. This new method of approaching drug discovery and even drug design relies heavily on computational power, and shifts the scientist's efforts from basic laboratory research to virtual drug discovery research. A major change in drug discovery involves the virtual study of bioactive molecules and the design of drug candidates that have attributes similar to those of known bioactive compounds. These technologies are commonly known as molecular modelling and computational chemistry. The recent technological advances have changed the face of drug discovery beyond recognition. New compounds in developed world can now be synthesized in unprecedented numbers via combinatorial chemistry, matched by ultra-high throughput screening of unparalleled speed and scope (Nkunya, 2002**)**.

This is different from most developing countries which are still in traditional technologies in which few new compounds take long time to be obtained from natural products and seldom from synthesis. It must however, be realised that until recently, combinatorial chemistry has been divorced and almost in opposition to the traditional structure activity relationship (SAR) lead synthesis programmes (often termed rationale design) (Wright *et al.,* 2001*)* A further evolution is now occurring, combining the synthetic and screening revolution, but with the high speed synthesis directed by emerging SAR in a "closed loop," thus allowing rapid optimisation of chemical matter. In addition, the sequencing of the human genome has started its own, very costly, highly competitive and resource consuming race to assign function to novel genes. The industry will need to change the way discovery and development work together to succeed in an increasingly uncertain environment.

Developing countries lack deliberate technological learning and implementation of technological policies that are in line with domestic health and economic problems. Also overwhelming is the third world countries continuous failure to

learn and copy from the newly industrialized countries and to address properly the key issues that have shaped the development paradigms in these countries. The only way to counter such a polarity is by building local research and development and production capacity through technology transfer so as to generate long-term solutions as well as sustainable economical development. Though costly, efforts have to be made to create enabling environment in third world countries to allow smooth transfer of capacities. Deliberate initiatives in technological learning and implementation of technological policies that are in line with domestic health and economic problems are very crucial for technological advancements.

Lack of trained multidisciplinary human resources

Despite the availability of funds and modern technology, successful drug discovery and development requires highly trained, multidisplinary manpower and well focused management. Human resources needed for drug discovery and development are ethnobotanists, biotechnologists/biochemists, medicinal chemists and pharmacologists. Medicinal chemists who are engaged in drug discovery are part of interdisciplinary teams, and must therefore understand not only the field of organic chemistry, but also a range of other disciplines to anticipate problems and interpret developments to help move the project forward (Nwaka & Ridley, 2003). A pharmacologist tests the candidate drug in human beings following the stages of clinical trials. It is a matter of concern that, qualified medicinal chemists and biotechnologists/biochemists together with pharmacologists are still not available in many institutions concerned with drug research in developing countries. This is a serious problem and urgent measures need to be instituted to fill the gap. One reason for their insufficient may be due to brain drain as they are highly needed in pharmaceutical firms in the developed world.

Issues of management are also very serious in that there is lack of targeted plans to create enabling environments for both technological development and transfers, prioritisations with the same meagre resources and lack of plans for capacity building of human resources in the areas of drug discovery and development. Thus, improvement of working conditions, advance planning for human resource development and prioritisation for the meagre resources need no emphasis for developing countries advancement in drug discovery and development.

Way Forward

The process of drug discovery and development involves diverse disciplines; focused management, technological advancement and large amount of resources need to be poured in, for delivering the success. Majority of the developing countries lack much of these pre requisites and as such they are highly undeveloped in the field. In order to enhance contributions to research and development of new drugs, priority should be accorded to at least five domains. These are human resources development, increased investments in science and technology, establishment and strengthening of suitable institutions, formulation and adoption of appropriate policies and inter-country cooperation within and outside the third world countries.

Science and technology as a tool is well known for its greater contributions to the effective development of research and development, which in turn gives a greater push to economic development. At the moment, third world countries have neither capacity nor favourable infrastructures for utilizing genomic information for new drug discovery and development, and to these countries, ethnobotanical information is still a realistic and most deployable source of new drugs. On this regard, reliable inventories on herbal remedies need to be established to guide drug research work.

Despite the small resources in terms of funding, developing countries need to prioritise on drug discovery but for longer time than a normal course of drug discovery and development. However, clear knowledge on length of drug discovery process has to be learnt by the leaders so as to make plan on resource delivery systems and to avoid despair due to long processes in terms of time. As part of human resources development, these countries also need to back drug discovery investment polarity by establishing and strengthening local research and development and production capacity through training and technology transfer as among important and feasible tools to produce long-term solutions as well as sustainable economical development.

Developing countries, therefore, need to strengthen research on efficacy and toxicity testing of herbal remedies so that at the time of establishment, disease burden is reduced by the use of such remedies. It is a matter of concern by some scientists that traditional herbal remedies stand a better chance of staying for years without any resistance being developed than the modern medicines (W. Spitteler, *per comm*). This idea necessitates the re-invention of the wheel back to herbal remedies subjected to efficacy and toxicity testing. Motivation of scientists in terms of both earnings and working environment may counteract the movement of trained resources to search for greener pastures in the developed countries

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