Building Capabilities for Regional Production of Quality-Assured Medicines in Africa

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Abstract:
International Donor Agencies currently budget several billion USD annually to provide health care to sub-Saharan Africa. One major form of this aid is the provision of medicines at reduced or no cost to low-income populations. Two major areas must be substantially improved in order for national governments to be equal contributors in managing this assistance; [1] National Drug Regulatory Authorities must take over responsibility for assuring the quality of medicines, and [2] medicines purchased with donor money but be made regionally, rather than being imported from outside of Africa, with a resultant, crushing, negative impact on regional production. We seek to address these areas by creating appropriate technology for regional production of quality-assured medicines and by teaching national Drug Regulators how to inspect and assure the quality of medicinal products. As these objectives become reality, a significant reduction in the true cost of medicines will also occur, since the very expensive burden of oversight will be shifted from high-income to lower-income countries.

1. Introduction - Background

The Global Fund for AIDS, Tuberculosis and Malaria (GFATM, 'Global Fund') was founded in 2002 to expand access to essential medicines in Less Developed Countries (LDCs)[1]. This program has catalyzed the emergence of a global framework for drug management and procurement for access programs. In total, several billion US dollars from several major International Donor Agencies (IDAs) are now available annually for this purpose[2]. International Donor Agencies encourage increased access either by directly purchasing and distributing medicines for less-developed countries, or through grants for this purpose[3]. Essentially all access medicines, however, are purchased from providers located outside of Africa. Oversight for these programs (procurement, quality assurance, testing, shipping, inspection and regulation) is also handled almost exclusively by entities located in high-income countries[4]. IDAs, moreover, do not provide funding for the development of local/regional industry or for training of National Drug Regulators. Three significant, negative impacts on industrial development and the healthcare sector in sub-Saharan Africa result from these practices.

1. African National Drug Regulatory Agencies (NDRAs) do not regulate Access Programs, as they are considered incapable of exercising effective oversight

2. The African Pharmaceutical Industry faces huge obstacles for survival, growth and access to local markets, because Access Programs purchase foreign-made products to compete with their goods

3. The real price of access medicines is much higher than the apparent "price per unit", because of the invisible costs associated with external systems of drug management (eg, WHO PreQualification Program, PEPFAR, UNITAID, GDF, UNICEF and GAVI)

A pharmaceutical industry does currently exist in sub-Saharan Africa. In Tanzania and Kenya alone (eg,) there are respectively forty-three and thirty-nine registered pharmaceutical companies[5]. These companies do not possess the capacity to meet all regional needs for medicines, but they are very important for the growth of regional independence and sustainable public sector development. The long-term desirable state is one in which regional production of medicines provides for the needs of sub-Saharan Africa. The common external perception of African pharmaceutical production is unfavorable with respect to drug quality, price and availability[6]. We believe that regional drug production in sub-Saharan Africa is technologically achievable, can be cost-competitive, and can assure the quality of drugs produced in compliance with all international standards. This paper describes our efforts in (a) training African pharmaceutical professionals in quality-assured drug production and (b) the creation of new technologies for drug production that are inexpensive, environmentally benign, and appropriate for use in sub-Saharan Africa.

Experimental Design

2. The Framework for Global Pharmaceutical Production

Our educational efforts at the Industrial Pharmacy Training Unit (IPTU) at the St. Luke Foundation/Kilimanjaro School of Pharmacy are centered on training professional people in the current best-practice production of modern medicines. Medicines production is comprised of two significantly different sets of technologies. Active Pharmaceutical Ingredients (APIs) are drug molecules. Drug molecules are the ingredients of a medicine that exert the desired therapeutic effect upon human dosing. APIs are produced from much less expensive raw materials. Most APIs are produced by chemical reactions – the creation of new bonds between atoms, creating complex, biologically-active molecules from basic chemicals. Some APIs are produced by fermentation technology – the use of enzymes or whole-cell organisms for the production of drugs by biologically-catalyzed transformations. APIs are almost always unsuitable for human use "as-is" for a variety of reasons. APIs are combined with a number of additional ingredients (excipients) and undergo further processing (eg, granulation, milling, compression, coating) to provide a finished dose form. Finished dose forms are the presentation forms (eg, tablet, capsule, oral solution) of medicines that a patient takes. A key operational thought is that the API remains the same – no bonds are made or broken – during the production of finished dose forms. The production of APIs represents a disproportionate share of the cost of medicines; 65-80% of the overall cost of a finished dose form is usually due to the cost of API[7]. The production of APIs, however, requires an additional level of industrial sophistication beyond manufacturing finished dosage form. Although a number of LDCs (Thailand, Bangladesh, Pakistan) have growing capabilities to produce finished dose forms, only a few (India, China, Russia, Brazil) presently practice large-scale production of APIs. New drugs are originally developed and launched by global, originator pharmaceutical companies – often known collectively as "Big Pharma." Generic drugs contain the same API as originator companies, but often differ somewhat in their finished dose form composition. Generic APIs and finished medicines in LDCs often originate from India or China. Although many companies in these countries sell products with good quality, many others do not.

3. Quality-Assurance and Drug Regulation

The quality of drugs is an important issue in LDCs. Common, international approaches to assuring the quality of medicines have been established. Both API and finished dose form production is carried out under the Guidelines known as Current Good Manufacturing Practices (cGMP)[8]. Process validation, cGMP and the demonstration of bioequivalence are the basic requirements to assure the quality of both originator and generic drugs. Quality assurance means that products are reproducible from batch-to-batch and that generic medicines are proven to possess equivalent performance with originator products. The cGMPs include the requirements that drug production operates under a system of quality management, that all drugs are tested to ensure they meet appropriate specifications, and that drug manufacturers are periodically inspected by independent regulatory agencies to ensure their adherence to the Guidelines. Most LDCs lack the resources and experience to provide the required level of oversight to ensure the quality of medicines within their national sovereignty. Under these circumstances, counterfeit and substandard drugs are found in commerce, to the detriment of public health.

Quality is assured for medicines by the prior approval of both producers (Companies) and specific products (medicines) by competent NDRAs. Drug Regulatory Authorities that have demonstrated acceptable competencies for drug inspection and approval are known as Strict Regulatory Authorities (SRAs). The WHO PreQualification Program (WHO PQ) and the US FDA are examples of SRAs. International Donor Agency programs will only purchase products that have been approved by SRAs. The only NDRA in sub-Saharan Africa that has qualified as an SRA is that of the Republic of South Africa[9]. The longer-term objectives of GFATM and related programs include the transfer of responsibility for the regulation of medicines to National oversight in LDCs. A major reason for lack of progress towards this objective is that Donor funds are not used to train African drug regulators, to upgrade the standards of NDRAs, or to train African pharmaceutical companies in drug development and cGMP.

This paper presents our experiences (2006 – 2010) with helping to encourage the production of quality-assured medicines in sub-Saharan Africa. One of our activities is training African pharmaceutical professionals in the full range of requirements to produce medicines with assured quality. Our objective is to enable African pharmaceutical companies to achieve WHO PQ status and for NDRAs in sub-Saharan Africa to achieve SRA status. A second major undertaking of our efforts is to create new, appropriate technologies that will maximize the ability for regional production of quality-assured, cost-competitive medicines in Africa.

Results and Discussion

4. Industrial Pharmacy Education

One of us (Ekeocha) has established an Industrial Pharmacy Teaching Unit (IPTU) at the Kilimanjaro School of Pharmacy / St. Luke Foundation in Moshi, Tanzania (SLF / KSP)[10]. We have subsequently put in place a comprehensive Program to teach the fundamentals of quality drug production. This Program consists of four, two-week courses that participants take over a time span of approximately twelve to eighteen months. The heart of the Program is modeled after the Industrial Pharmacy program at Purdue University[11]. This is possibly the top-ranked program of its kind. The program was originally designed to meet the needs of Global, Originator Pharmaceutical Companies for training their employees. World-class experts in drug discovery, development and clinical trials contributed to the contents of this curriculum. Contributors from the pharmaceutical industry, drug regulation (US FDA), patents (law firms) and academics have further tailored the program for the needs of African

pharmaceutical professionals. Participants in the Program are selected from pharmaceutical companies, NDRAs and Universities, based on having a substantial background of academic training and professional experience. This program utilizes intensive classroom training, team exercises and hands-on product development in a laboratory that has been designed and built for this purpose. At the end of the Program, participants are able to develop new drug products, determine meaningful tests and set appropriate specifications to assure quality. Participants are also able to utilize these skills to detect substandard and counterfeit medicines. Participants also understand how to meet International standards for Quality Assurance and cGMP, and are able to write a product submission dossier that is approvable by the WHO PQ or other SRA.

5. Content and History of the IPTU Curriculum

Each course in the Industrial Pharmacy program has approximately seventy-five hours of contact time. About forty-five hours is devoted to classroom instruction, while the remainder is divided between team exercises, examinations and laboratory work. Three instructors are available full-time during the length of each course. Each course is roughly equivalent to four University credit hours in an MSc or PhD program. The four courses are sequenced to provide a full overview of the drug discovery and development process, with a heavy emphasis on cGMP, drug product development, API synthesis and production of drugs with assured quality in courses two through four. Upon completion of the curriculum, students are issued a Professional Certificate attesting to their relevant expertise in drug development and quality medicines production. The first course in the curriculum was conducted in July, 2008. The first "graduating class" of nine students finished in March, 2010 with another fourteen students completing in August, 2010. Currently, thirty-two students are enrolled in the next course planned for March, 2011; this represents roughly our maximum enrollment given the current instructional format. UNIDO (United Nations Industrial Development Organization) has funded tuition and travel for many participants in this program. UNIDO has been particularly helpful in planning for future expansion of these efforts to make the IPTU self-sustaining. Future expansion of our course offerings includes (a) four additional courses into the curriculum to provide for an MSc degree and (b) intensive, three-day targeted course offerings for specific issues in the industry such as analytical methods validation, documentation and writing Standard Operating Procedures.

6. The Drug Development Laboratory – Construction, Use and Contribution to Sustainability

The German GTZ (Gesellschaft fur Technische Zusammenarbeiten) has supported our efforts very generously, providing roughly €500,000 for construction, equipment (up to 50L scale) and the commissioning of a drug development laboratory. Laboratory work is most heavily concentrated in the third course; students engage in about thirty hours of laboratory practice in this course, making Active Pharmaceutical Ingredients (APIs) and finished dosage forms. Participants are guided through the design of a matrix of experiments and the evaluation of experimental outcomes to identify critical process parameters, optimize variables and arrive at a process for a finished dose form. In the August, 2009 Laboratory exercise, participants actually prepared API by chemical synthesis (amodiaquine, a common malaria drug) and used this API for preparing their finished dose form.

A scheduled upgrade of the Development Laboratory is planned in order to bring the facility into full compliance with cGMP guidelines. By providing students with a hands-on exercise that is fully cGMP-compliant, trainees will have the complete package of training needed to implement these standards in their own companies. A further advantage of attaining cGMP

status for the IPTU, however, is sustainability. By producing cGMP products (even though on a modest scale) the IPTU is aiming to be able to sell these products to the Tanzanian government, funded by International Donor Agencies. This small-scale production will fund the activities and expansion of the School, while operating in a cyclical fashion. As the technology for one product is mastered and incorporated into cGMP approvals at regional companies, the IPTU will switch to other high-priority products, thereby enabling the successive mastery of multiple critical medicines for regional production.

7. Cost Competitiveness of Regional Production and New Technology Development

An issue that remains to be addressed is the cost-competitiveness of African industry. International Donor Agencies have policies that emphasize cost as the primary consideration when choosing between competing producers of quality-assured medicines. The generic pharmaceutical industries in some countries (particularly India and China) have benefited from a large, well-trained workforce, government investment in growing a national pharmaceutical industry, increasingly reliable and inexpensive sources of power and easy access to raw materials from a local fine chemicals industry. The economy of scale for medicines production is also a factor that weighs in favor of cost competitiveness for producers in India and China. Although these present varying degrees of difficulty, they do not necessarily exclude producers in sub-Saharan Africa from being cost-competitive. The differential tax duties levied on imported medicines (often as much as 12.5%) in African countries provide a mitigating factor in favor of national production. The low prices and modest profit margins of essential medicines for the first-line treatment of HIV/AIDS, tuberculosis and malaria, moreover, make these products unattractive for producers in China and India. With the growth of a substantial middle-class population in these countries, the small profit margins for these drugs make them of lower priority than selling drugs for hypertension, diabetes, cardiovascular indications and cancer with higher profit margins in regional markets. Because of this, we believe that African production of essential medicines can be cost-competitive with imported drugs.

An additional factor that favors local production is the Global Fund provision that African countries can "set aside" portions of their support from the Global Fund to deliberately purchase locally-produced medicines that have been approved by a Strict Regulatory Authority[12]. Although locally-produced medicines in sub-Saharan Africa have achieved WHO PQ for only two companies (Aspen Pharmacare and Sandoz in South Africa)[13], multiple additional companies have submitted dossiers to the WHO PQ for this purpose. Quality Chemicals, located in Uganda, recently received a satisfactory inspection for cGMP operations filed as a Public Inspection Report by the WHO PQ Program (WHOPIR) as a necessary pre-condition to WHO PQ approval of individual products[14]. It is worth noting in this regard, that only five Chinese companies have received WHO PQ approval for their products at the time of this writing (September, 2010).

8. New Technology Development

A final factor that can help pharmaceutical companies in sub-Saharan Africa achieve cost competitiveness with existing manufacturers is new technology. It is evident that companies who have already absorbed the investment required to enter a market have a cost advantage over those who are entering the field. We have attempted to even this disparity by discovering new technology for the less expensive, environmentally benign production of critical medicines on the WHO Essential Medicines List using new chemistry. The synthesis of amodiaquine API is an example of this. The commercial synthesis of amodiaquine is a four-step process that proceeds through paracetamol[15]. We have developed a simplified

synthesis of amodiaquine that qualifies as an example of "Green Chemistry". This synthesis is only two steps long and proceeds from the same starting materials as the commercial route. The overall yield is approximately 95%, versus the approximately 65% overall yield of the commercial synthesis from p-aminophenol. Additionally, our modified synthesis eliminates the use of polar, aprotic solvents and utilizes only water and 2-propanol (rubbing alcohol) as solvents. The amount of 2-propanol required is approximately 3 kg/kg of product produced. We have additionally developed "green" chemical syntheses of piperaquine and lumefantrine that will be discussed in more detail during our public presentation.

9. Conclusions and Future Directions

Our approach to encouraging regional production of quality-assured medicines in sub-Saharan Africa has three major components: [1] the creation of new, appropriate technologies for production of critical medicines, [2] Industrial Pharmacy education to teach professionals the means of meeting Strict Regulatory Authority guidelines for pharmaceutical production, and [3] achieving sustainability for our efforts by creating a cGMP center for both education and small-volume sales of quality-assured medicines. Success has currently been demonstrated by the graduation of twenty-three individuals with Certificates in mastery of cGMP and drug development. New technology has been successfully created for API and dose-form production that is appropriate for regional production. The production of API and finished product has been demonstrated in the IPTU development laboratory. The next step is to bring the facility into full cGMP compliance in order to sell small volumes of quality-assured products into regional markets, thereby assuring the sustainability of the ongoing enterprise.

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