FORUM FOR AFRICA-BASED PHARMACEUTICAL MANUFACTURERS AND POTENTIAL INVESTORS

"SETTING THE SCENE"

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Table of Contents

Acknowledgements

This report has been made possible by funding from the Global Fund to fight AIDS, TB, & Malaria.

The author would like to acknowledge all those companies and organisations that participated in the information gathering exercise, especially those who completed the questionnaires circulated and those who freely gave of their time for follow-up questions and clarifications.

The author would also like to acknowledge the valuable advice given by the Forum Steering Group in the preparation and finalisation of the paper, as well as their help in contacting organisations to complete the questionnaires and input to the information gathering process.

Executive Summary

This paper has been prepared as a pre-read for the Forum for Africa-based Pharmaceutical Manufacturers and Potential Investors, to be sponsored by ALMA, the Global Fund, MMV, & RBM Partnership. The Forum aims to bring together manufacturers and potential investors or technical collaborators and facilitate communication between them. The paper is a neutral and fact-based summary of the current situation and aims to act as a starting point for a discussion, using antimalarials drugs (and ACTs specifically) to illustrate the situation.

In 2010, the Global Fund started to pilot a new initiative to increase the availability of ACTs in malaria endemic countries – AMFm. This, along with the increased use of ACTs following changes to WHO Malaria Treatment Guidelines, has seen the global market for ACTs grow to its current level of 245 million courses *per* year. This is however expected to decline slowly in the coming years due to the success of prevention measures (like bednets) and wider use of diagnostic tests to stop the use of antimalarials to treat non-malarial fevers.

Pharmaceutical manufacture is a complex process. Because the ultimate product will be used to treat sick people who may die or suffer severe health effects if not treated properly, high standards are expected throughout the manufacturing and distribution process to ensure that the risk to the patient from sub-standard drugs is reduced to an absolute minimum. These standards are encapsulated in the principles of Quality Assurance and Good Manufacturing Practice. Pharmaceutical manufacturers who wish to become eligible to supply their products to programmes financed by international aid money (*e.g.* Global Fund grants, PMI programmes) must show that they are meeting these international standards. The global standard is either for the product in question to be Pre-qualified by the WHO or to be approved by a Stringent Regulatory Authority. For Africa-based companies, Pre-qualification is the normal route. Pre-qualification applies internationally agreed standards for quality in order to ensure that "poor people do not receive second rate drugs", and to minimise the risks that sub-standard versions do not reduce the viable lifespan of a drug (*e.g.* by encouraging the development of resistance by the parasite). This is especially of concern with ACTs because of their value in fighting malaria.

With the launch of AMFm, access by manufacturers of ACTs that are not prequalified to the market for antimalarials in the private sector – where Africa-based manufacturers have conventionally concentrated – will be severely curtailed. AMFm, is reducing the price to patients of ACTs to that of chloroquine and other cheap but now ineffective antimalarials. Africa-based manufacturers who wish to continue to manufacture antimalarials (and ACTs in particular) will need to address a series of key issues to remain viable:-

- Developing a large enough market for their products. All manufacturers questioned recognised that this needed to be on at least a regional basis, if not pan-African.
- Being able to access this extended regional market – by ensuring proper regulatory approvals, building a robust distribution system, and avoiding excessive costs from customs duties and tariffs.
- Being price and cost competitive. The major international manufacturers are producing on the scale of 10 or 100 millions of treatments *per* year and this gives them large economies of scale and purchasing power with raw material suppliers. In addition, Novartis and sanofi aventis are both supplying on a "no profit / no loss" basis, which makes it more difficult to match their prices. Asian manufacturers are often supported by export subsidies from their national governments.
- Quality standards – as mentioned above unless manufacturers can meet international quality standards, then they will not be eligible to supply to programmes that constitute more than 90% of the antimalarial market.
- Manufacturers need to be able to produce and deliver their products reliably and to a pre-agreed schedule. Breakdowns in the supply of raw materials, stoppages due to problems with machinery or utility supplies, or batch failures all can result in late or non-delivery, with risks to the company's reputation and ability to gain future business.

Challenges and barriers identified by Africa-based manufacturers to being able to access the important antimalarial market were:-

- Sourcing raw materials (APIs) and excipients reliably and at prices that allowed for a competitive price at the end of the process. In particular, the volatility of artemisinin supply and therefore prices was highlighted.
- The maintenance of the specialised machinery used in pharmaceutical manufacture and obtaining spare parts in a timely way was also highlighted. The cost of this could also be burdensome.
- Ensuring reliable supply of electricity and water to keep the production process running and to ensure adequate air conditioning and waste disposal for production and storage facilities.
- Finding, employing, and training staff to the standards needed to operate a high quality facility.
- The "no profit / no loss" strategy by major manufacturers was seen as a major barrier to Africa-based companies being able to access tenders and orders financed by international organisations or initiatives (like AMFm).
- Quality standards applied and the need for Africa to conform to international standards was widely questioned. It was seen more as an economic barrier designed to exclude African manufacturers than a necessary requirement for patient safety. Clinical bioequivalence studies needed to achieve Pre-qualification was the most difficult requirement to meet.
- Access to affordable finance to support the necessary investment to enable Africa-based companies to meet international standards was another challenge identified.

African governments were urged to take more action to collaborate regionally, establish and properly resource regional regulatory & enforcement systems, reduce or remove tariffs to promote the flow of products through their regions, and ensure transparency in drug procurement processes. Legal frameworks needed to be assessed, gaps filled, and overlaps removed. A proper industrial policy to promote pharmaceutical manufacture was needed (across a region if necessary), particularly if the current level of aid funding might reduce in the future.

The international community was challenged to make up its mind on whether to support the concept of Africa-based manufacture or not. There had been too much talking with little action, and major players were still unconvinced and calling for more research into the issues. Finance to upgrade both manufacturing facilities but also regulatory and enforcement agencies was requested. Technical support from WHO needed to be improved and QA standards better justified. Major funders, especially the Global Fund, should allow for local production premiums to be charged or allocate a proportion of demand to local manufacturers in order to promote Africa-based production.

Finally three possible scenarios are outlined in this paper, with some indication of their implications. They are:-

- *No Support*: most interested parties decide that it does not make sense to develop an Africa-based pharmaceutical industry
- *Continue Limited Support*: the current situation of no consensus, limited initiatives, and a lot of discussions on the subject continue.
- *Clear Support*: there is a widespread consensus that developing an Africa-based pharmaceutical industry is worth pursuing on health, social, economic, and developmental grounds. A clear strategy is developed, all stakeholders buy-in, and all the necessary resources are made available to make this successful. This would be a long-term commitment from all concerned.

Background

The African Leaders' Malaria Alliance (ALMA) - in collaboration with the Global Fund to fight AIDS, TB, & Malaria (Global Fund), the UN Secretary-General's Special Envoy for Malaria (Special Envoy), the Medicines for Malaria Venture (MMV), the Roll Back Malaria Partnership (RBM), and UNIDO are convening a Forum for Africa-based Pharmaceutical Manufacturers and Potential Investors. This Forum is being convened in the context of evolving reactions to the start of the Affordable Medicines Facility – malaria (AMFm), hosted by the Global Fund. Some manufacturers in Low Income Countries (LICs) have expressed to the Fund and RBM fears about eligibility for their artemisinin-based combination therapies (ACTs). The basis for these fears is that only products from manufacturers that meet the Fund's quality standards can be co-paid by the AMFm. This is a long-standing issue, which has attracted even greater attention because of the AMFm. ALMA and its co-convenors of the Forum acknowledge the concerns expressed by manufacturers based in Africa, but they do not have a mandate to provide any direct assistance to manufacturers. However they would like to facilitate communication between manufacturers and potential investors or technical collaborators.

This background document is designed to be a neutral and fact-based introductory summary of the situation with regard to the manufacture of ACTs as it currently exists and applies to Sub-Saharan Africa. It does not aim to advocate any particular position with regard to the feasibility of manufacturing antimalarials in Africa. Although the information it contains is primarily concerned with ACTs, most of its contents could also apply to other antimalarials, and even other essential drugs that are needed for diseases that are a public health priority in Africa. It has been compiled from publically available data sources (referenced in the document) and from the answers to questionnaires sent to interested parties during the preparations for the Forum. The objective of the document is to be a starting point for discussion and to give all participants a basic level of understanding of the issues and challenges that may be raised during the Forum.

The document is divided into the following sections:-

Market for ACTs: a brief summary of the current estimates of the market opportunity.
The Manufacturing Process: a brief and simple overview of the inputs, facilities, and infrastructure needed for a pharmaceutical factory to manufacture oral ACTs. This introduction is for readers not conversant in pharmaceutical manufacturing and its special challenges.
Quality Assurance and Good Manufacturing Practice: an introduction to the key concepts that govern the thinking behind the quality standards and principles being used by major international purchasers and funders of antimalarial treatments.
Quality Standards & Regulatory Approvals: an introduction to the standards being used by the major international purchasers and funders.
Requirements for a Viable Manufacturing Business: a summary of the factors that must be considered in setting up a viable manufacturing business that can supply ACTs and other products.
Challenges & Barriers for Manufacturers: an overview of the main challenges faced by pharmaceutical manufacturers in Africa in trying to build a business that is viable but also meets international quality standards. These have been identified by the respondents to the questionnaires circulated prior to the writing of this report.
Roles of Governments and International Bodies: a summary of the requests from respondents to the questionnaires on the roles that governments and international bodies should take on to promote manufacture in Africa.
Future Scenarios and Implications: some possible scenarios based on the level of support for manufacture in Africa and their potential implications.

Market for Artemisinin-containing Combination Treatments

Since the adoption of ACTs as the recommended first-line treatment for *P falciparum* malaria, the market for these drugs has grown substantially. The most recent forecasts estimate global demand for ACTs in 2011 at 245 million treatments (range 200 – 310)[1]. Approximately 90% of *P falciparum* cases are reported to be in Sub-Saharan Africa[2], leading to an estimated market for ACTs in Africa of 220 million treatments in 2011. In the future, this is expected to decline slowly due to a combination of factors[3]:-

- More widespread use of bednets will reduce the number of infections (especially in children under-five and pregnant women);
- More widespread use of pre-treatment diagnosis (as now recommended by the WHO[4]) will reduce the number of antimalarial treatments used to incorrectly treat non-malarial fevers.

The rate of decline is difficult to predict due to the many factors that need to be considered and this will vary country-by-country. RBM, UNITAID, and the Global Fund are co-ordinating efforts to develop forecasting models that give a better understanding of the future demand for ACTs.

The launch of AMFm has extended the application of the low prices agreed by international manufacturers from the public sector to the private sector. Manufacturers like Novartis and sanofi aventis have set these prices on the principle of "no profit, no loss". Roughly speaking, the average price *per* course of treatment is at or below US$1. This means that the value of the market for ACTs to manufacturers is currently about US$245 million, with US$ 220 million being attributable to Africa.

The Manufacturing Process[5]

The generic pharmaceutical manufacturing process for an oral (tablet) product is shown in Fig. 1 (Figures are to be found in the relevant section at the end of the paper). The following sections outline the key inputs and considerations needed for each stage, using ACTs in general (and artemether – lumefantrine in particular) as examples. Fig 3 shows the various stages in the process and their approximate timing.[6]

Active Pharmaceutical Ingredients

Artemisinin Derivatives

The three artemisinin derivatives needed to manufacture the ACTs recommended by the WHO[7] are artemether, artesunate, and dihydroartemisinin. All three are manufactured by chemical transformation of artemisinin itself. This is extracted from the leaves of the *Artemisia annua* plant. The plant is mainly grown in China and Vietnam, although other growing sites have been established in East Africa and Madagascar. The Artepal project has identified 94 manufacturers of artemisinin derivatives around the world[8]. Of these, only 5 are in

[1] MIT-Zaragoza Forecasting Task Force. Global ACT Forecasts for 2010-2011. Artemisinin Conference; 2010 Oct 12-14; Antananarivo, Madagascar. [Accessed 2011 03 Feb] Available from: http://www.mmv.org/sites/default/files/uploads/docs/artemisinin/2010_Madagascar/ACT_forecasts.pdf
[2] World Health Organisation. World Malaria Report 2009. Geneva: WHO, 2009: 27.
[3] Johansson EW, Cibulskis R, Steketee R. Malaria Funding & Resource Utilisation: the First Decade of Roll Back Malaria. Geneva: Roll Back Malaria Partnership, 2010: 27
[4] World Health Organisation. Guidelines for the Treatment of Malaria. 2nd ed. Geneva: WHO, 2010: 9.
[5] This section draws extensively on: Bennett W, Cole G, editors. Pharmaceutical Production – an engineering guide. Rugby: Institute of Chemical Engineers, 2003
[6] Rietveld H. Meeting the needs of children with malaria. Presentation to the All Party Parliamentary Group on Malaria: London, 23 March 2009 [accessed 2010 10 Dec]. Available from: http://www.appmg-malaria.org.uk/text.aspx?id=10
[7] World Health Organisation. Guidelines for the Treatment of Malaria. 2nd ed. Geneva: WHO, 2010.
[8] Artepal.org. Inventory of API manufacturers. [Accessed 2010 10 Dec]. Available from: http://www.artepal.org/index.php?option=com_content&task=blogcategory&id=37&Itemid=97

Africa, and another 18 outside China and Vietnam. In the Far East, the seeds must be planted in January – March of each year and it is 7 months before the plant has matured enough to extract reasonable quantities of artemisinin. Conversion of the extracted artemisinin into the derivatives needed for ACT manufacture takes around 3 months. Artemisinin yields of ≈2% weight from dried leaf are currently considered reasonable, although efforts are in place to increase the yield of *Artemisia annua* plants[9]. Major manufacturers of ACTs have established long-term agreements with growers and extractors to ensure adequate supplies to meet their demand forecasts. In the absence of such agreements, ACT manufacturers must source artemisinin or its derivatives on the open or "spot" market. Prices here fluctuate widely depending on the supply-and-demand situation. In recent years they have varied between US$ 170 and US$ 1,100 per kilogram.

A method to produce artemisinin semi-synthetically is in development and will start to supply commercial quantities in the 2nd half of 2012. This will not depend on the growing season of the plant for the production cycle. However the aim of developing this process is only to supplement (not supplant) plant-based production and to stabilise supply[10].

Non-artemisinin Derivatives

The other active ingredients (APIs) needed for ACTs are all fully synthetic chemicals. Currently those required by the WHO Malaria Treatment Guidelines[11] for oral ACTs are lumefantrine, amodiaquine, piperaquine, sulphadoxime, pyrimethamine, and mefloquine. They are sourced from specialised pharmaceutical API manufacturers, who are able to produce the compounds to the required quality standards and specifications required for drug manufacture. At the moment, only one South African company has limited capacity to manufacture APIs, and so these must be sourced from manufacturers predominantly in India or China (but may also include Europe or North America).[12]

Excipients

Excipients are the non-active components of a Finished Pharmaceutical Product (FPP). For example, the non-active components of Coartem® (artemether + lumefantrine) are colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, and polysorbate 80.[13] A manufacturer must be able to source supplies of pharmaceutical grade excipients to be in compliance with the quality standards required for drugs to be used in humans. As with APIs, these are not readily available from African suppliers and must be sourced from companies predominantly in India or China (but may also include Europe or North America).

Formulation (Secondary Production)

Formulation is the process of combining the APIs and excipients together to produce the form of the product that is actually administered to the patient (tablet, injection, topical cream, *etc.*). In Fig. 1, it is usually understood to include the stages of mixing and granulation, drying, tablet pressing, and coating. As will be

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[9] For example: CNAP Artemisia Research Project. [Accessed 2010 10 Dec]. Available from: http://www.york.ac.uk/org/cnap/artemisiaproject/index.htm

[10] Cutler M, Ellman A. Presentation of Key Findings. Artemisinin Conference; 2010 Oct 12-14; Antananarivo, Madagascar. [Accessed 2010 10 Dec]. Available from: [http://www.mmv.org/sites/default/files/uploads/docs/artemisinin/2010_Madagascar/Presentation_of_key_findings.pdf]

[11] World Health Organisation. Guidelines for the Treatment of Malaria. 2nd ed. Geneva: WHO, 2010. See also Annex 3.

[12] Berger M, Murugi J, Buch E, IJsselmuiden C, Moran M, Guzman J, Devlin M, Kubata B. Strengthening Pharmaceutical Innovation in Africa. Council on Health Research for Development (COHRED), New Partnership for Africa's Development (NEPAD); 2010: 34.

[13] Rx List. [Accessed 2010 10 Dec]. Available from: http://www.rxlist.com/coartem-drug.htm ; electronic Medicines Compendium [Accessed 2010 10 Dec]. Available from: http://www.medicines.org.uk/emc/medicine/9196/SPC/#EXCIPIENTS

mentioned later, this is the stage where great care is needed to ensure that there is no cross-contamination between different APIs, which could lead to avoidable adverse events in patients.

During the development of the FPP prior to its regulatory approval, the details of this process will have been worked out, standardised, and documented. Statistical process control techniques will have been built into key stages of the process so that regular quality control sampling takes place throughout. This continuous monitoring of the process ensures that adverse trends in the manufacture of a particular batch can be picked up early and remedial steps taken. Comprehensive records are maintained to ensure there is an audit trail for every batch of product in case of a problem during manufacture or when the product has been distributed to patients.

This stage of production is normally carried out using specialised machines that start with the raw APIs and excipients, mix them, and then (for tablets) compact and coat them prior to secondary packaging operations. Equipment required for this stage will include blenders, milling machines, roller-compactors, fluid-bed dryers, tablet compressors, and tablet coating machines. The exact machines used will depend on the exact formulation being manufactured.

Packaging (Tertiary Production)

Packaging is the stage of manufacture when the tablets (or other formulation) are put into packaging to protect the tablet *etc.* from damage (see Fig 1). This can be physical (to prevent breakage or similar damage) or environmental (temperature, exposure to air, humidity, *etc.*). The need to properly protect products from the environment is particularly important in malaria-endemic countries. Here FPPs may be exposed to considerable variations in temperature and humidity, especially prolonged periods at high temperatures. The lack of good "cool chain" facilities between the production factory and the end-user exacerbates this challenge. The primary packaging (the first line of protection) of tablets is usually a foil or blister pack. This must be able to give adequate protection from humidity and air and the choice of metal foil or plastic laminates to be used in this is an important part of the development process. Equally important is to confirm that the primary packaging does not itself interact with the tablets, reducing their shelf-life.

Because of the importance of patient safety, packaging and packaging methods have become increasingly important and sophisticated in recent years. Manual assembly of finished products is giving way progressively to more automated methods. The modern packaging line incorporates handling and sensing equipment designed to minimize human intervention and eliminate human error.

Secondary packaging is the assembly of the correct number of primary packs (blisters, foils, *etc.*) into a carton or other container, along with the required patient and doctor information leaflets. Increasingly patient communication is important to ensure that the product is properly used, and so patient information leaflets or similar packaging components have been developed. For example, the Coartem® blister packs have been developed especially to properly communicate to patients and carers how the product must be taken (see Fig 4).

Machinery used in this stage of production is often combined so that tablets can be delivered in at one end and products cartoned and packaged into shipping containers emerge from the other end. Machinery is often specially designed to meet the needs of the facilities and the products to be manufactured. Automatic labelling is increasingly used to ensure that batch details and expiry dates are properly attached to the products, to ensure a proper manufacturing audit trail, and to remove human error.

Facilities

Even simple pharmaceutical manufacturing and packaging processes must be carried out in areas with controlled environments. Regulatory authorities will be looking at the following factors to ensure that the production facilities are adequate:-

- the avoidance of cross-contamination;
- product segregation;
- material and personnel flow;
- waste treatment;
- utility services (water, electricity, *etc.*);
- maintenance systems;
- QC test facilities;
- cleaning procedures;
- environmental classification;
- heating, ventilation, & air-conditioning (HVAC) systems;
- surface finishes;
- lighting selection.

In the case of manufacturing operations, even where products require similar levels of product protection, separate environmental and spatial arrangements are usually necessary to prevent cross-contamination. It is, therefore, usual for manufacturing and primary packaging processes to be conducted in product specific environments. It is essential for such processes where any degree of cross-contamination is hazardous to the product or patient to be separated physically, as a minimum. Production processes involving especially clean conditions for product exposure (such as for parenteral, ophthalmic or inhalation products) add further complexity to the environmental and space planning activity. Ventilation and air handling systems are a common problem in causing cross-contamination and therefore facility design must account for this. Cleaning protocols to avoid cross-contamination between batches using the same machinery are critical and also must be properly documented.

It is common practice to group final packaging operations, which usually involve the handling of products in a partially enclosed condition (such as filled and capped bottles, tablet blister packs) in a single room with limited spatial separation between linked groups of machinery, but with a common ventilation system. However, ensuring that there is no cross-contamination between different products here is also critical and appropriate protocols must be put in place and their use recorded.

The construction of pharmaceutical facilities also will require proper attention being given to the maintenance and cleanliness of the manufacturing spaces. This is where the correct selection of surface finishes, ventilation systems, and cleaning protocols are important. For example, joints in walls and ceilings are normally coved so as to minimise the risk of contaminants getting stuck in the joint and to allow for easier cleaning.

Some chemicals used in manufacture that are safe in the concentrations found in the final product may still be harmful when exposed in high concentrations during formulation. This places a high responsibility on manufacturers to ensure that operatives in the factory are properly protected from these risks. Such protection may come from adequate ventilation systems or from the use of proper protective clothing and equipment, as well as good manufacturing procedures.

Manufacturing facilities must have adequate storage facilities to allow for APIs, excipients, bulk tablets, packaging materials, FPPs, *etc.* to be stored securely and under quarantine. Quarantine is necessary to allow for quality control sampling and testing to be properly carried out with no risk that the untested material can be used in and/or contaminate the manufacturing process. Given the need to maintain APIs, excipients, quarantined and finished products in the correct environmental conditions (as set out in the manufacturing

and product specifications), storage facilities need to be properly air-conditioned. This is especially true in areas of high temperature and humidity – like Africa.

Pharmaceutical factories must also have adequate testing laboratories on the premises. These laboratories are necessary for the routine quality control testing of samples from batches at various stages of the manufacturing process. They may also be involved in process improvement projects or to validate new testing methods. The specific requirements and the equipment required in a particular laboratory will depend on the exact nature of the products being produced in each factory.

Equipment that is used for pharmaceutical production and laboratory testing is usually specialised and only available from specialist equipment supply companies. The location of these specialist companies or their agents relative to the pharmaceutical plant will determine how easy it is to properly maintain the equipment while avoiding lengthy and costly downtime. They often require specialist technicians to maintain them and another important factor is how quickly the supplier or their representative can have an engineer available when problems arise.

In order to keep all the various parts of the manufacturing facility operating properly and without unnecessary disruption, it must have uninterrupted access to electricity and water. If a production run is stopped because of an interruption in the power supply, Good Manufacturing Practice (GMP – see below) may well require that this batch is rejected and production start afresh with new raw materials, with the accompanying impact on the cost of manufacture. The impact of an unreliable power supply was recently highlighted as a problem for one Ugandan factory trying to reach global quality standards.[14] Water supplies must also be of a certain minimum quality to allow it to be easily purified for use in pharmaceutical manufacturing processes. Again interruption in supply may result in batches having to be rejected.

Staff

A wide range of technical skills are needed in the workforce of a successful pharmaceutical factory. These include pharmacists, analytical chemists, microbiologists, laboratory technicians, engineers, as well as skilled manufacturing technicians and operatives who directly work on product manufacture. A well-trained and skilled workforce is needed both for the skills they bring to the organisation, but also so they can quickly understand what they need to do **and why**. A pharmaceutical manufacturing operation needs to ensure that they have a reliable supply of these skilled workers.

Staff training is crucial to the successful running of a safe and effective pharmaceutical factory. It not only teaches them the correct procedures that they must follow but also enables them to understand the reasons behind them. For example, staff have to be properly trained in something as apparently simple as how to clean machinery between batches. Every individual operator would use their own method of cleaning if they were not trained. Their individual methods will vary from time to time and there is no guarantee that any of the operators' methods will provide cleaning to the standards required to reduce the risk of contamination to an acceptable minimum. Therefore standard cleaning protocols must be established, staff trained to follow them, and adherence monitored and recorded.

[14] Taylor J, Bate R, Putze E, Tren R. The push for local production, costs, and benefits – a case study of Uganda's Quality Chemicals. Africa Fighting Malaria Policy Paper; September 2009.

Quality Assurance & Good Manufacturing Practice

Quality Assurance[15]

Quality Assurance (QA) is a wide-ranging concept which covers all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made to ensure that pharmaceutical products are of the quality required for their intended use. QA therefore is an integral part of all key activities throughout the pharmaceutical manufacture, distribution, and procurement process. Because pharmaceutical products are administered to sick people, they are not ordinary commodities of trade and require special attention. It is not considered adequate to rely on random sampling for quality control checks as allowing one defective tablet through may have serious consequences for a patient. In this sense pharmaceutical products are not like other consumer products. QA aims to build in quality to products, rather than simply relying on quality control checks at the end of the manufacturing process, which may be acceptable for ordinary commodities of trade. Its principles and requirements have been developed over several decades and are codified by various technical and regulatory organisations (*e.g.* World Health Organisation).

QA systems are required to avoid the risk of sourcing substandard, counterfeit, or contaminated pharmaceutical products, leading to complaints about products and product recalls, wastage of money and serious health risks to patients. Such problems affect the credibility of procurement agencies, cause financial losses, and (most importantly) put patients' safety in danger.

Good Manufacturing Practice

Good Manufacturing Practice (GMP) is defined as[16]:

> "That part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use."

As with the principles of Quality Assurance, the aim is to build in quality rather than simply relying on testing to ensure quality. It is a system devised to ensure that products are consistently produced and controlled according to pre-established quality standards. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated by simply testing the final product. The main risks of poor manufacturing practice include unexpected contamination of products causing damage to health or even leading to death, incorrect labelling that could lead to patients' receiving the wrong medicine, and, last but not least, insufficient or excess active ingredient that contributes either to ineffective treatment or to adverse effects.[17]

The common general requirements that run through virtually all the GMP codes worldwide are[18]:-

- the establishment and maintenance of an effective quality assurance system;
- proper control of the process;
- personnel that are suitably qualified, trained and supervised;
- premises and equipment that have been located, designed, installed, operated, and maintained to suit intended operations;

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[15] World Health Organisation. A model quality assurance system for procurement agencies. Geneva: WHO; 2006. WHO Technical Report Series, No. 937, 2006 (Annex 6)

[16] European Medicines Agency. [Accessed 2010 10 Dec]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000154.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580027088&jsenabled=true

[17] Arayne MS, Sultana N, Zaman MK. Historical incidents leading to the evolution of good manufacturing practice. Accred Qual Assur 2008; 13: 431-432

[18] Welbourn J. Good manufacturing practice. In: Bennett W, Cole G, editors. Pharmaceutical Production: an engineering guide. Rugby: Institute of Chemical Engineers, 2003: 17-37

- maintenance of adequate records of all aspects of the process so that in the event of a problem being identified, an investigation can trace the complete history of the process, including how, when, and where it was produced, under what conditions and by whom (*i.e.* an audit trail);
- the prevention of contamination from any source, in particular from components, environment, premises and equipment by the use of suitable premises and equipment and through standard operating procedures.

Quality Control

Quality Control (QC) means all measures taken, including the setting of specification sampling, testing and analytical clearance, to ensure that starting material, intermediate, packaging material, and FPPs conform to established specifications for identity, strength, purity and other characteristics. It is the check step in the overall Quality Assurance process. Based upon statistical sampling techniques, samples are taken at appropriate stages in the manufacturing process and tested to ensure that they meet the specifications for that stage. This QC sampling is usually undertaken at the end of the particular stage and not during the actual process.

Quality Control is to assure the professional user or ultimate consumer that every batch of a product conforms to quality standards, fulfils the label claim, and meets all legal requirements. However, alone it is only the testing of products or intermediates after they have been through or all of the manufacturing process. The QA philosophy requires that there must be a total dedication to building quality and reliability into every product by the proper design of the entire manufacturing process. The adoption of GMP complements QC processes in maximising the assurance to the end-user of the high quality of the product in question.

Quality Standards & Regulatory Approvals

Pre-Qualification Programme (WHO-PQ)

The United Nations Pre-Qualification Programme was set up in 2001 and is managed by the WHO. Its Vision is "Good quality medicines for everyone." It aims to achieve this Vision through the strategic elements of:-

- Unified standards of acceptable quality, safety, and efficacy.
- Comprehensive evaluations of the quality, safety, and efficacy of medicinal products, based on information submitted by the manufacturers, and inspection of the corresponding manufacturing and clinical sites.
- Prequalification of quality control laboratories for pharmaceuticals.
- Building the capacity of staff from national regulatory authorities, quality control laboratories, and from manufacturers or other private companies, to ensure medicines quality.

Pre-Qualification (PQ) follows the process shown in Fig 2[19]. The first step in the prequalification process consists in the joint issuing, by the WHO Prequalification Programme, other UN agencies (UNAIDS and UNICEF) and UNITAID, of an Invitation for Expression of Interest (EOI). EOIs focus on products that have been identified by the respective WHO disease departments as vital to effective treatment and to expanding treatment programmes. Currently, this means products for treating HIV/AIDS, tuberculosis (TB), and malaria, and for reproductive health. Every product contained in an EOI is already included on the WHO Model List of Essential Medicines and/or in WHO treatment guidelines.

Any manufacturer/applicant wanting to participate in the prequalification process has to submit the relevant product dossiers for those products listed in the current Invitation for Expression of Interest they want to be assessed. In the case of Africa-based manufacturers, these products will normally be generic versions of established antimalarials, normally referred to as "multisourced". The WHO sets out the format that these

[19] Procedure for prequalification of pharmaceutical products. In WHO Expert Committee on Specifications for Pharmaceutical Preparations: 43rd Report. WHO Technical Report Series 953. Geneva: WHO; 2009: 131-148

Product Dossiers should take. The information required to be included in a multisourced product dossier must include:-

- Details of the product;
- Marketing authorization status
- For the API(s):
    - properties of the API(s);
    - sites of manufacture;
    - route of synthesis;
    - specifications;
    - stability testing;
- For the FPP:
    - formulation;
    - sites of manufacture;
    - manufacturing procedure;
    - specifications for excipients;
    - specifications for the FPP;
    - container/closure system(s) and other packaging;
    - stability testing;
- Product information:
    - summary of product characteristics;
    - package leaflet;
    - labelling;
- Summaries on:
    - quality;
    - biopharmaceutics (interchangeability).

The multisource generic products must be shown, either directly or indirectly, to be therapeutically equivalent to the comparator product if they are to be considered interchangeable. Full details are set out in "Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part",[20] which provides recommendations on the quality information for active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs) that should be submitted to WHO to support product dossiers. This document is worth studying as it shows the level of detail required by WHO-PQ to ensure that the FPP in question meets globally acceptable quality standards. These standards are global to avoid any risk of "poor people being supplied with second class products". The challenge for many manufacturers is to be able to supply the level of information on their FPPs and manufacturing methods required by the WHO-PQ assessors. The most burdensome requirement for most Africa-based manufacturers is the need to show bioequivalence in human clinical studies to ensure that the FPP in question is interchangeable with the comparator product. These may be[21]:-

- comparative pharmacokinetic studies in humans, in which the active pharmaceutical ingredient (API) and/or its metabolite(s) are measured as a function of time in an accessible biological fluid such as blood, plasma, serum or urine to obtain pharmacokinetic measures, such as AUC and C_{max} that are reflective of the systemic exposure;
- comparative pharmacodynamic studies in humans;
- comparative clinical trials;
- comparative *in vitro* tests.

[20] World Health Organisation. Guideline on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product (FPP): Quality Part. Geneva: WHO, 2010

[21] Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In WHO Expert Committee on Specifications for Pharmaceutical Preparations: 40th Report. WHO Technical Report Series 937. Geneva: WHO; 2006: 347-390

The quality assessment is undertaken to evaluate whether the pharmaceutical product being evaluated meets the requirements recommended by WHO, and is manufactured in compliance with GMP. The procedure established by WHO for quality assessment incorporates:-

- general understanding of the production and quality control activities of the manufacturer;
- assessment of product data and information on safety, efficacy and quality submitted by the manufacturer, including product formulation, manufacture and test data and results;
- assessment of the manufacturing site's adherence to GMP, and its consistency in production and quality control of starting materials, with specific emphasis on active pharmaceutical ingredients, and finished product;
- assessment of clinical testing units or organizations (i.e. parties performing one or more clinical trials with the product) for compliance with good clinical practices and good laboratory practices, as appropriate;
- random sampling and testing of medicines supplied.

Once WHO is satisfied that quality assessment has been completed for the manufacturer of the relevant starting materials, the finished pharmaceutical product, and the clinical testing units, and that the product meets WHO recommended standards, the product (as produced at the specified manufacturing site) is added to the WHO List of Prequalified Products. This is published on the WHO website[22].

The WHO prequalification of medicines process can take as little as three months, provided the data presented are complete and demonstrate that the product meets all required standards. If the data are insufficient, however, the process can take considerably longer since the manufacturer must submit the necessary additional data for reassessment. To ensure that prequalified products continue to meet WHO specifications, WHO-PQ regularly re-inspects manufacturing sites of prequalified products. It also evaluates any changes (known as "variations") made to specifications, manufacturing processes and quality control of prequalified products, and conducts random quality control tests on sampled prequalified products.[23]

Stringent Regulatory Authorities (SRAs)

Stringent Regulatory Authorities[24] will normally require similar types and levels of information on FPPs as are required by the WHO-PQ Programme. There may be differences to take into account such as their local legal frameworks and specific local situations. Applications for marketing authorisations in these countries are designed to allow the product to be sold there, and so may not be relevant for diseases that predominantly affect the developing world.

In recent years, the European Medicines Agency (EMeA) has introduced procedures under which products that will be used exclusively outside its area of jurisdiction can still be assessed. The procedure is called “Article

[22] WHO List of Prequalified Medicinal Products. [Accessed 2010 10 Dec]. Available from: http://apps.who.int/prequal/default.htm

[23] World Health Organisation. Prequalification of medicines by WHO: Fact Sheet 278. Geneva: WHO, Aug 2010. [Accessed 2010 10 Dec]. Available from: http://www.who.int/mediacentre/factsheets/fs278/en/index.html

[24] The national drug regulatory authorities which are members, observers, or associates of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) are normally considered to be “Stringent”. These countries are: European Union member States (Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, The Netherlands, and United Kingdom), Japan, United States, Switzerland, Canada, Australia, Norway, Iceland, and Liechtenstein. ICH was formed in 1990 to rationalise and harmonise regulation between the USA, European Union, and Japan. Other countries and WHO have joined as observers or associates. See http://www.ich.org/home.html for details of ICH, its membership, and its work.

58".[25] Medicines eligible for this procedure are used to prevent or treat diseases of major public health interest. This includes medicines for WHO target diseases such as HIV/AIDS, malaria, or tuberculosis. The EMeA's Committee for Medicinal Products for Human Use (CHMP) carries out a scientific assessment of applications submitted under Article 58, and, after consultation with the WHO, adopts a scientific opinion. This opinion is based on the evaluation of an application containing data on the quality, safety, and efficacy of the product, and concludes on the benefit-risk ratio of the product. It is to the same standard as for an application for marketing authorisation in the European Union (EU) without going through the final steps to grant such an authorisation. Applicants must be established legally in the EU. A Certificate of a Medicinal Product is issued for a product that has received a positive CHMP scientific opinion under Article 58. The certificate certifies that the medicinal product has been evaluated for quality, safety, and efficacy by the EMEA. It can then be supplied to a regulatory authority in another country as evidence of the review by the CHMP.

Canada has adopted a similar process under the S.C. 2004, c. 23 (Bill C-9) procedure.

However most Africa-based manufacturers will not be seeking SRA approval for their products and so these procedures need not be described in further detail in this paper.

Requirements of Global Agencies

The largest funders of purchases of antimalarial commodities (including drugs) on a global basis are the Global Fund and the US President's Malaria Initiative. In 2009, the Fund reported contributions of US$ 925 million (approx 25% on treatment) and PMI of US$ 511 million (approx 30% diagnosis & treatment).[26] The World Bank Booster Program for malaria control (2005-15) is ten-year programme with a target of US$ 1.5 billion in assistance to country malaria control programmes. UNICEF is one of the largest purchasers of such commodities and often buys on behalf of national malaria control programmes. In 2010 it purchased around 41 million ACT treatment courses[27]. Therefore, their requirements on drug quality standards are very important in determining the size of the market for ACTs and other antimalarials that a manufacturer can access.

Global Fund to fight AIDS, TB, & Malaria (Global Fund)

The Global Fund's Quality Assurance Policy[28] lays out the quality standards that must be met by manufacturers in order for their products to be eligible to be purchased with Global Fund grant money. In summary, FPPs must either be on the WHO List of Prequalified Products or have approval from an SRA. In cases where there is an urgent need for an FPP that does not meet these criteria, a time-limited *interim* approval (6 or 12 months) to purchase can be granted by an Expert Review Panel (ERP). The ERP is convened by WHO Health Systems & Services. It reviews the potential risks/benefits associated with the use of FPPs that are not yet WHO-prequalified or SRA-authorized and then make recommendations to the Global Fund on whether to allow grant funds to be used to procure such FPPs. In order to qualify for an ERP review, the FPP in question must come from a factory that has been accredited as GMP standard either by the Pre-Qualification Programme, an SRA, or a regulatory authority participating in the Pharmaceutical Inspection Cooperation Scheme (PIC/S).[29]

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[25] European Medicines Agency. EMeA Procedural Advice on Medicinal Products Intended Exclusively for Markets Outside the Community Under Article 58 Of Regulation (EC) No 726/2004 in the Context of Co-Operation with the World Health Organization (WHO). London: EMeA; 01 April 2009. Doc. Ref. EMEA/534107/2008

[26] World Health Organisation. World Malaria Report 2010. Geneva: WHO; 2010: 12, 148-163

[27] Blasco J. UNICEF Update on ACT Procurement; 2010 Oct 12-14; Antananarivo, Madagascar. [Accessed 2011 01 Feb]. Available from: [http://www.mmv.org/sites/default/files/uploads/docs/artemisinin/2010_Madagascar/UNICEF_update_on_ACT_procurement.pdf]

[28] Global Fund to fight AIDS, TB, & Malaria. Global Fund Quality Assurance Policy for Pharmaceutical Products (as amended on 10 November 2009). Geneva: The Fund, 2009. [Accessed 2010 10 Dec]. Available from: [http://www.theglobalfund.org/documents/psm/Annex1-%20FullTextRevisedQualityAssurancePolicy_en.pdf]

[29] List of PIC/S members is available on the PIC/S website. http://www.picscheme.org [Accessed 2010 10 Dec].

US President's Malaria Initiative (PMI)

PMI gives preference in purchasing antimalarials to FPPs that are approved by the US Food and Drug Administration (FDA). PMI will also procure FPPs that are WHO Pre-Qualified, or approved by another SRA. If a required drug cannot be found that falls into these three categories, PMI will then source the FPP through international suppliers in whom they have confidence to supply GMP standard products to the highest quality possible, and subjects every batch of drugs to quality testing from an independent ISO-17025 certified laboratory.[30]

World Bank

The quality requirements for products purchased with World Bank funds (under the Booster Program) are similar to those used by both the Global Fund and PMI. Antimalarial drugs must be approved by WHO-PQ or by an SRA. The Bank requires at least two suppliers to be able to tender for contracts. If there are not two manufacturers whose product are WHO-PQ or SRA approved, then additional bids can be sought from suppliers who have applied for WHO-PQ or SRA approval and manufacture in GMP-compliant facilities. If these requirements cannot be met, then bids can be entertained from manufacturers who manufacture in GMP-compliant factories (based on inspection by WHO or an ICH or PIC/S member).[31]

UNICEF

Any product purchased by UNICEF must generally be authorized for marketing in the country of origin. Upon request, a proof of compliance with WHO's GMP guidelines must be supplied in the form of a certificate issued by an internationally recognized authority. Alternatively, a GMP inspection may be carried out by UNICEF or a representative chosen by UNICEF. UNICEF is an Observer to the PIC/S scheme which allows it to carry out these on-site GMP inspections, although it does not issue GMP certificates[32].

Requirements for a Viable Business

This is a brief outline of the main requirements that need to be achieved if an Africa-based pharmaceutical business can be made to be viable. It is not possible to quantify many of these factors as they will vary too greatly between individual company situations – size and quality of current facilities, size of current business, attitude of current investors, *etc.*. This section is intended only to give pointers to the major factors to be considered as a business case or commercial plan is developed. This section includes input from respondents to the information-gathering questionnaires.

Adequate Market Size

- Whether-or-not a manufacturer can earn a return on its investments will depend principally on the sales it can achieve. This in turn depends on the size and nature of the market it is trying to access. All manufacturers identified that a single country in Africa could not be large enough to support a business with international quality standards. At least they would have to plan to sell to a regional market (*e.g.* EAC, ECOWAS).
- The market for ACTs will segment in the future into three:-
    - Public sector: sales to government, NGOs, and similar organisations, usually through large tenders and contracts. In many cases these purchases may be made through international purchasing agents (like UNICEF or the Global Fund's Voluntary Pooled Procurement) or the organisation's global purchasing system.
    - Private sector: sales to private hospitals, clinics, and drugstores (often through wholesalers).

[30] Personal communication.

[31] Procurement Policy and Services Group, World Bank. Malaria Booster Control Program: Procurement and Supply Management. Washington DC: The International Bank for Reconstruction and Development / The World Bank; 2006: 5. [Accessed 2011 04 Feb]. Available from: http://siteresources.worldbank.org/EXTAFRBOOPRO/Resources/Malaria-Toolkit.pdf

[32] UNICEF Standards for Supplies. [Accessed 2011 04 Feb]. Available from: http://www.unicef.org/supply/index_9323.html

- AMFm (for ACTs): sales to private hospitals, clinics, and drugstores (often through wholesalers) but at a subsidised *ex*-manufacturer price that allows patients to access these drugs at prices equal to or lower than existing but not longer effective antimalarials. To achieve this lower price, the design of AMFm incorporates three elements: (1) price reductions through negotiations with manufacturers of ACTs; (2) a buyer subsidy, via a co-payment to the manufacturer at the start of the global supply chain; and (3) support of interventions to promote appropriate use of ACTs.[33]

- If the AMFm is rolled out globally, because it requires prequalified products, it will have a significant negative impact on the size of the non-AMFm private sector market, where most Africa-based manufacturers have focused to-date. Therefore they will need to sell into the AMFm market if they are going to be able to ensure a market size that has manufacturing volumes that allow their businesses to remain viable.

Accessibility to Market

- All companies surveyed recognised the need to be able to sell into a regional market to ensure that they had a target market size large enough for their business to be viable. However this means that finished products will need to be registered in all the countries in the relevant region, according to the various requirements of each country concerned.
- Companies must have developed distribution networks that will allow their products to be shipped first between the country of manufacture and the destination, and then within the destination country. This movement of goods may be by road, rail, air, or sea. Costs of transportation will vary between mode of transport and distance/difficulty involved.
- Moving products across borders may involve the payment of tariffs and duties. These will also vary between countries and regional economic zones. If they are significant, then this will be a major barrier for the company to access that country's market.

Competitive Price & Cost Structures

- If AMFm is fully implemented in the next few years, then the *ex*-manufacturer price that will apply to markets will be the public sector price. This in turn is likely to be determined by the prices charged by the big international manufacturers (including Indian and Chinese companies), who are often working on either no profit / no loss basis, for small percentage margins, or receive export subsidies from their national governments. Currently the target ex-manufacturer price *per* adult treatments is around US$ 1.56 for artemether/lumefantrine and US$ 1.00 for amodiaquine/artesunate.
- In the absence of a special premium for manufacture in Africa or in a region or single country, Africa-based manufacturers must be able to match these prices being charged by the major international players to be competitive.
- Most respondents to the questionnaires saw the antimalarial business as being a small profit generator for their business. This also implied that they would want to be able to maximise their volumes in order to minimise their *per* unit fixed costs. Therefore access to the major public sector and AMFm markets for antimalarials is the key to achieving viability.
- Major international manufacturers are already operating on a large scale (Novartis – 100 million treatments / year: see below). This gives them both large economies of scale in the allocation of their overheads. They are also able to negotiate long-term supply agreements with API suppliers (especially for artemisinin derivatives) that will give them costs below the "spot" market price. Africa-based manufacturers will either have to be able to establish similar agreements to bring the price of their artemisinin derivatives in line with the major players, or find cost-savings elsewhere in their manufacturing and supply chain.

[33] AMFm Task Force of the Roll Back Malaria Partnership. Affordable Medicines Facility – malaria (AMFm): technical design. November, 2007. http://www.rollbackmalaria.org/partnership/tf/globalsubsidy/AMFmTechProposal.pdf (accessed 2011 01 February)

Quality Standards

- All international funding and development bodies surveyed were united in the need to apply international quality standards to drugs purchased with their funds. Therefore Africa-based companies must upgrade their facilities to achieve the necessary certification (*e.g.* Pre-Qualification) in order to be able to access this major segment of the market. As-and-when AMFm is rolled out across Africa, the size of the market where international quality standards do not apply will become very small and maybe not viable.

Reliable Manufacture and Supply Chain

- Once a company has managed to meet all the requirements of the market on quality, price, delivery terms, *etc.*, and is able to win orders for its products, then it must still be able to supply its products according to the agreed delivery schedule. Failure to do this can severely damage the reputation of the company in question and may lose it future business.[34]
- Africa-based manufacturers must therefore be able to ensure that they can reliably obtain supplies of raw materials (APIs, excipients, packaging, *etc.*) in time to meet production schedules. One way to reduce the risk in this respect is to hold large stocks of materials, but this will add to the cost of manufacture.
- Manufacturers must also be able to access reliable supplies of electricity and water to ensure that their manufacturing can proceed in a predictable and cost-effective manner. Interruptions in these will lead to added costs and potentially missed delivery dates.
- Once the product has been manufactured and the necessary quality tests have been carried out to allow it to be released from the factory, then the manufacturer needs to have a reliable way of supplying it to the customer. This is not only a question of being able to physically move the product between the factory and the customer's storage facility, but also to be able to control the environment that the product is transported and stored in at levels of temperature, light exposure, and humidity in line with the product specifications and storage requirements.

Challenges & Barriers for Manufacturers

This section summarises the key challenges and barriers for Africa-based pharmaceutical manufacturers to being able to supply ACTs profitably to meet the market need, especially the major market segment funded by international aid (Global Fund, PMI, World Bank, *etc.*). This section includes the concerns of the respondents to the questionnaires.

Sourcing APIs & Excipients

- There is only one manufacturer of APIs based in Africa (Fine Chemicals Corporation, Cape Town), but they do not manufacture antimalarial APIs.[35] Therefore non-artemisinin APIs must be sourced from other API suppliers predominantly in India, China[36] (but may also include Europe or North America). This is normally done through agents or brokers and so availability may not be reliable. Because the scale of manufacture of African companies is smaller than international ones, the price that can be obtained by an African manufacturer is often higher than one based elsewhere with higher volumes.
- Sourcing lumefantrine, sulphadoxime, pyrimethamine, and amodiaquine may be reasonably straightforward as they are well established APIs and demand is recognised in the market. However there may be challenges in sourcing the non-artemisinin components of the newer ACTs – piperaquine

[34] Kangwana BB, Njogu J, Wasunna B, Kedenge SV, Memusi DN, Goodman CA, Zurovac D, Snow RW. Malaria Drug Shortages in Kenya: A Major Failure to Provide Access to Effective Treatment. Amer J Trop Med Hyg. 2009; 80(5), 737-738.

[35] Fine Chemicals Corporation Product List. [Accessed 2010 10 Dec]. Available from: http://www.fcc.co.za/Product-FullList.aspx

[36] Mhamba RM, Mbirigenda S. The drugs industry and access to essential medicines in Tanzania. Harare: Training and Research Support Centre, SEATINI, Rhodes University, EQUINET; 2010 Jul. EQUINET Discussion Paper Series 83.

(and in the future pyronaridine). These newer components will only become readily available once there is a well-established demand for them, and this will depend on their uptake by malaria control programmes and inclusion in various treatment guidelines.

- Production of artemisinin derivatives is dominated by companies based in China and Vietnam, although there are increasing amounts available from East Africa and Madagascar. Africa-based manufacturers need to be able to set up long-term supply agreements with one-or-more suppliers to avoid having to buy on the "spot" market. Here the market price can fluctuate wildly depending on the supply-and-demand situation, and these fluctuations can change the cost-of-goods of an ACT from competitive to uncompetitive quite quickly. Spot market prices of artemisinin have varied in the last 5 years from a peak of US$ 1100/kg in 2005 to a low of US$ 170/kg in 2007. Current forecasts for 2011 are in the range of US$ 400 -450/kg.[37]
- Sourcing of all APIs will usually be invoiced in US dollars or a similar internationally accepted currency. Currency fluctuations between the US dollar and the national currency of the manufacturer may affect the local cost of manufacture and the profit that can be earned.

Factory Equipment & Utilities

- Pharmaceutical manufacturing machinery is complex and specialised. It is only available from a small number of specialised manufacturers, not based in Africa. Access to spare parts and to maintenance engineers may not be quick or easy in Africa. Delays in getting machinery repaired when it breaks down will shut down parts of the manufacturing process and so add to the costs of an Africa-based manufacturer. Large scale companies may be able to have adequate engineering support on-site.
- As mentioned above, a reliable supply of electricity is essential to the smooth and cost-effective running of a pharmaceutical manufacturing plant. Supply interruptions will cause batches to be rejected, with the impact on total costs, and reduce the factory's ability to produce in the most efficient manner. Reliance on the frequent use of generators (even just for back-up) is not considered cost-effective.
- As with electricity, a reliable supply of reasonable quality water that can be consistently purified to the standards needed for pharmaceutical manufacture is essential. In Tanzania, water considered adequate to drink contains many impurities which must be removed before it can be used in pharmaceutical manufacture[36]. These additional purification costs put manufacturers at a disadvantage compared to those in other countries with higher quality supplies.
- Especially in countries with high ambient temperature and humidity levels, reliable air-conditioning systems in all parts of the factory, including the storage areas is essential. This is because the APIs and excipients, as well as the work-in-progress and the finished products, may well be damaged if either is allowed to rise above certain levels set in the product specifications. Normally API and excipient manufacturers will instruct buyers to keep the material in a closed container (to protect it from the light and humidity) and "in a cool place" (to protect it from heat). Compromising of API and excipient quality will lead to materials or batches having to be rejected, with the associated impact on cost of goods.
- Sourcing on a reliable basis the reagents and test standards needed to run the QC laboratories necessary in a GMP accredited factory can also be a challenge in countries with limited number of laboratories and so limited demand on the fine chemical and reagent suppliers.

[37] Pilloy J. Artemisinin Market – Quantities & Pricing; 2010 Oct 12-14; Antananarivo, Madagascar. [Accessed 2011 01 Feb]. Available from: [http://www.mmv.org/sites/default/files/uploads/docs/artemisinin/2010_Madagascar/Artemisinin_Market_Quantities__Pricing.pdf]

Staff Standards & Training

- The shortage of adequately educated and trained human resources in the African health sector (including the pharmaceutical industry) has been well recognised[38]. In a recent report[36], the Executive Director of TPI (Tanzania Pharmaceutical Industries) is quoted on this topic:-

> "Pharmaceutical industries are challenged by the difficulty developing a constant quality concept among the technical staff in the factories, which demands artisans with a mind set to handle the precision machines."

Economies of Scale

- Novartis have production capacity to manufacture 100 million Coartem® courses of treatment *per* year[39]. One may assume that sanofi aventis have similar capacity to manufacture Coarsucam® (amodiaquine – artesunate FDC). At this scale of manufacture, both can command significant economies of scale which will help to reduce their cost-of-goods. The other 4 manufacturers (based in India and China) currently eligible to participate in AMFm do not have this level of capacity, but it is reasonable to assume that they are operating at a scale of tens of millions of treatments per year. Where the companies have made a commitment to supply antimalarials on a no profit / no loss basis, large economies of scale do not increase a company's profits, but allow it to supply below the price a company that needs to make a profit on its products is able to charge. The challenge for Africa-based companies is to be able to establish a scale of manufacture that allows a cost of goods and ex-factory price that is competitive with the large global manufacturers. In the case of artemether / lumefantrine, this would have to be under US$1.59 (24 x 20/120mg tab) which is the maximum ex-manufacturer price allowed under the current AMFm agreements for hospital packs.[40] As mentioned below, this price has been negotiated with manufacturers who are supplying on a no profit / no loss basis.

Market Scale

- As mentioned elsewhere, the market for antimalarials is reasonably large across the African continent but is fragmented across 40+ countries. Manufacturers need to be able operate on a regional basis to build up the economies of scale, but this can be difficult especially for the smaller ones.
- Each country has individual regulatory processes and marketing controls. Meeting them imposes additional costs and potential time delays. For example, if different countries require different labelling, then this will reduce the size of production runs and hence increase unit cost of goods.

Competitive Pricing

- With the launch of the AMFm mechanism, a set of maximum *ex*-manufacturer prices has been negotiated with the 6 companies currently eligible and willing to participate. These prices are in the public domain.[40] At present, in order to be able to access AMFm funding, Africa-based manufacturers will need to be able to match these prices. The major part of the cost of goods of an ACT is the artemisinin derivative. Hence it is important the Africa-based manufacturer can source artemisinin derivatives at a price that allows it to compete with these globally agreed *ex*-manufacturer prices for the finished ACT.
- The publication of the maximum *ex*-manufacturer prices for eligibility to participate in the AMFm mechanism is likely to lead to these prices being adopted as the maximum prices allowed for any publically funded anti-malarial purchases. It has been forecast that purchases of ACTs will make up

[38] The Health of the People: the African Regional Health Report. [Accessed 2010 10 Dec]. Available from: http://whqlibdoc.who.int/afro/2006/9290231033_eng.pdf

[39] Rietveld H. Are we delivering effective treatment to malaria patients? Presentation to the All Party Parliamentary Group on Malaria: London, 26 January 2010. [Accessed 2010 10 Dec]. Available from: http://www.appmg-malaria.org.uk/text.aspx?id=10

[40] http://www.theglobalfund.org/documents/amfm/RBM_ACT_Pricing_Fact_Sheet_en.pdf

90% of public sector purchases and 73% of private sector purchases of antimalarials.[41] As ACTs will remain unaffordable in the Private Sector in the absence of the AMFm mechanism[42], the only *ex*-manufacturer prices that will be available to Africa-based manufacturers will be the Global Fund negotiated maximum prices.

- The public commitment to no profit / no loss pricing for ACTs by Novartis and sanofi aventis (at least), coupled with the high economies of scale and hence low prices they can charge, increases the challenges to an Africa-based manufacturer to be able to earn a return on any ACT sales it can make to the public or AMFm market segments.

Quality Standards

The major technical impediment to local manufacturers being able to fully participate in supplying ACTs is the need to meet international quality standards. It is interesting to see the difference in opinion between the Africa-based manufacturers and the international community. The manufacturers in general regard the quality standards and policies they are required to meet by internationally funded programmes as being as much an economic barrier as a requirement for ensuring patient safety. International organisations in general only see quality standards as being a requirement to protect the patient.

Most of the companies responding planned to try and get WHO-PQ approval for their antimalarials. Each company has a different set of challenges they need to meet. However several major challenges in common were identified:-

- Need for clinical bioequivalence studies for their versions of existing products rather than simple laboratory-based equivalence studies. This was both felt to be too expensive (poor return investment) and difficult in practice due to the poor clinical research infrastructure in most countries they could access.
- Documentation required by WHO-PQ. This was both that supporting describing the manufacturing process and also the in-process records.
- Upgrading of existing facilities to meet GMP and WHO-PQ requirements. The return on investment was often difficult to justify.
- Lack of an adequate supply of trained staff to fill the key technical roles required to meet international quality standards.

Access to Affordable Finance

- Most companies identified the need for cheap and long-term local finance to support the necessary investment needed to upgrade their facilities to meet international standards.

Role of Governments and International Organisations

This section also draws heavily on the responses from the various stakeholders in answer to the questionnaires circulated when gathering information and opinions for this paper.

Role of African Governments

Respondents identified the following roles that they felt African governments should undertake or expand in order to support local manufacture:-

- More regional collaboration and integration, especially of regulatory systems. No one country was seen as being large enough to support a national drug regulatory authority (NDRA) adequate to

[41] Dalberg Global Development Advisors. Affordable Medicines Facility - malaria (AMFm): Technical Design. Geneva: Roll Back Malaria Partnership; 2007: 13.
[42] Dalberg Global Development Advisors. Affordable Medicines Facility - malaria (AMFm): Technical Design. Geneva: Roll Back Malaria Partnership; 2007: 7.

ensure international quality standards. However regional collaboration to spread the cost, ensure sustainable funding, and share the available expertise could improve the situation. Mutual recognition of regulatory approvals and/or common requirements was also asked for. This is also reflected in the recent WHO Review.[43]

- Active development of an industrial policy to support local manufacture. This would include initiatives to improve the training and supply of technical staff, the building of adequate infrastructure (roads, utilities, communications), and suitable tax incentives for investment in quality facilities. An ambitious industrial policy around encouraging local pharmaceutical manufacture was thought to have both economic as well as health benefits.
- In order to allow companies to access regional markets, action on tariffs and customs duties will need to be taken to allow inexpensive movement of products between countries and so allowing for regionally based manufacturing.
- Some respondents felt that African governments were too prepared to be passive recipients of international aid when it came to health issues. They urged that governments needed to be more active in developing local industry so that they could become less reliant on aid and less exposed should the levels of aid fall in the future.
- Work to assess, clarify, and simplify the legal framework of regulation, which is seen as complex and difficult to implement. There are gaps and overlaps that need to be addressed. This was also identified in the WHO Review.[43]
- Ensure transparency in procurement of pharmaceuticals to ensure that manufacturers could be able to plan properly and justify investment proposals based on a "level playing field".
- More work to develop an African supply of artemisinin derivatives was recommended. This included both growing the *Artemisia annua* plant, the extraction of the artemisinin, and the conversion to the derivatives needed for ACT manufacture. This would reduce the reliance on supplies from China and Vietnam bought at high prices on the "spot" market, and allow for long-term supply agreements to be negotiated between the Africa-based manufacturers and the growers/extractors.
- More aggressive action on counterfeiting and sub-standard medicines was required. This is part of the need to properly resource NDRAs and their enforcement sections. Where sub-standard medicines are allowed to be widely available, this undercuts the economic viability of high quality manufacturers.
- Some respondents felt that African governments needed to challenge the requirements of the international community and make them justify the requirement for global quality standards.

Role of the International Community

Economic Development Organisations

- There was a strong feeling that international development organisations should make up their minds on Africa-based manufacture and "stop paying lip service" to its development. If there was general agreement that this made economic and developmental sense, there needed to be a proper strategy to ensure that companies could have access to their needs – financial, technical, and human. The international community has been debating on whether this is a sensible use of resources for many years. The conclusions of the World Bank paper[44] in 2005 that "In many parts of the world, there is no reason to produce medicines domestically since it makes little economic sense" and that "A research agenda should be created that is specifically designed to test assumptions about local production of pharmaceuticals" still have not been answered to the satisfaction of all stakeholders.
- Manufacturers should be required to rigorously justify their business cases for funding proposals. This will ensure that only those which have the best chance of succeeding are supported.

[43] World Health Organisation. Assessment of Medicines Regulatory Systems in sub-Saharan African Countries. Geneva: WHO; 2010. Report No.: WHO/EMP/QSM/2010.4

[44] Kaplan W, Laing R. Local Production of Pharmaceuticals: Industrial Policy and Access to Medicines. Washington DC: World Bank; 2005 01 Jan.

- If it is felt to be worthwhile supporting the development of Africa-based manufacture of ACTs and other pharmaceuticals, then financing to fund the upgrading of facilities to international standards need to be put in place and widely advertised. Access to these funds should be made as simple as possible and not be burdensome or complicated, with complex reporting requirements.
- Support of Africa-based artemisinin supplies was urged (see previous section).
- In addition to making cheap finance available to manufacturers, economic development organisations were urged to also make funding available to African governments in order to facilitate the industrial policy mentioned above, targeted specifically at the needs of the pharmaceutical industry.
- Financing to governments to allow them to upgrade their regulatory approval and enforcement systems was also urged.

World Health Organisation

- The WHO-PQ Programme needs to improve its ability to respond to enquiries and to support manufacturers who are trying to achieve Pre-Qualification. Common requests were for more training and mentoring, better response times to enquiries, and early warning on changes to requirements.
- Similarly the WHO needs to increase its support and technical assistance to NDRAs to raise their standards and identify problem areas. This would include help with sorting out issues with the legal framework that have already been identified in some cases.[36]
- There needs to be a better argued rationale for the quality standards that the WHO is seen to be applying. These are not considered realistic by many manufacturers in an African setting.

Global Fund

- The QA Policy is seen as a major impediment to local manufacturers being able to sell their products into programmes funded by the Fund. With the problems of justifying the investment needed to bring facilities to the standards required by WHO-PQ, it is unlikely that many manufacturers will be able to participate and this situation will only get worse as AMFm closes them out of the private sector as well as the public sector for ACTs. This is leading to political tensions in some countries that may put the roll out of AMFm at risk. Respondents felt that the Fund needs to either be more proactive at explaining the rationale for the QA standards it requires, or to relax the standards to allow GMP approved factories to supply drugs that may not have been given a positive WHO-PQ review.
- If the Global Fund is going to support the concept of promoting local manufacture, then it should explicitly allow countries to pay a “local manufacturing premium” to incentivise this or allocate a proportion of demand to local manufacturers. This may well conflict with the Fund’s current emphasis on value-for-money.
- It has also been suggested that the Fund should do more to support better demand forecasting in collaboration with the work being done by RBM and others. With better demand forecasting, it was suggested that some form of Advanced Market Commitment (AMC) could be put in place to support business plans to finance facility upgrades and expansion.

Future Scenarios & Political Implications

This section outlines three possible scenarios for local pharmaceutical manufacture in Africa with possible implications for the future:-

No Support

In this scenario, the international community (and maybe African Governments) decides that there is no economic or social case for supporting the development of an Africa-based pharmaceutical manufacturing industry – led by investment in essential drugs for Africa like ACTs and other antimalarials.

This scenario will probably lead to increased pressure from Africa-based companies on their local governments not to support programmes like AMFm, which directly affect their principal target market – the private sector. These programmes will be seen as favouring big international manufacturers at the expense of local companies. Quality standards will continue to be seen as barriers to entry rather than key requirements to ensure patient safety. If AMFm is successful as a model for expanding access to other key drug classes targeted as major health issues in Africa, further development of this concept could be put at risk by the opposition at the country level.

Reduction in access to quality antimalarials (especially ACTs) for the poorest and most needy segments of the population will potentially put at risk efforts to roll back malaria just at the time that significant gains have been made and progress towards elimination is being seen in a few African countries.

Alternatively, a clear decision that pharmaceutical manufacture is not viable at this time in Africa may give the necessary signals to investors and entrepreneurs that this is not an industry that they should be investing in. This would redirect their resources to other industries where there is a great possibility of success. There would be an initial outcry from existing manufacturers who stand to see their investments suffer.

Continued Limited Support

This is the current situation. There is no consensus on the economic case for Africa-based manufacture, with some organisations supporting the concept and others failing to see a robust enough case. There will continue to be meetings to discuss the possibility and a few initiatives to promote Africa-based manufacture. These will be disjointed and run the risk of not achieving very much. However no clear signal is being given to potential investors on the preferred way forward.

This scenario will lead to continued frustration among manufacturers and African governments. Access to global initiatives like AMFm will continue to be seen as favouring big international pharmaceutical companies and the concept of global quality standards will continue to be questioned as being appropriate for Africa. Africa-based manufacturers may pressure their governments not to support AMFm and similar programmes, leading to shortages of appropriate high quality medicines for the neediest segments of the population. This will have knock-on effects on the general efforts to roll back malaria by reducing the availability of the best medicines and running the risk of treatment failures.

Clear Support

In this scenario, the global community undertakes the necessary research and develops the necessary case to support investment in Africa-based pharmaceutical manufacture (as suggested in the 2005 World Bank Report[44]). The relevant international and regional development agencies develop co-ordinated plans and gather the necessary resources for the necessary investment. Where necessary, maybe through the offices of the African Union or one of the regional economic development agencies, African governments collaborate to harmonise regulatory, legal, fiscal, and other issues to maximise the opportunities for local manufacturers. Ideally a full strategic plan is developed from which all agencies can work. Issues of the barriers caused by international quality standards are negotiated with the relevant organisations to a satisfactory conclusion.

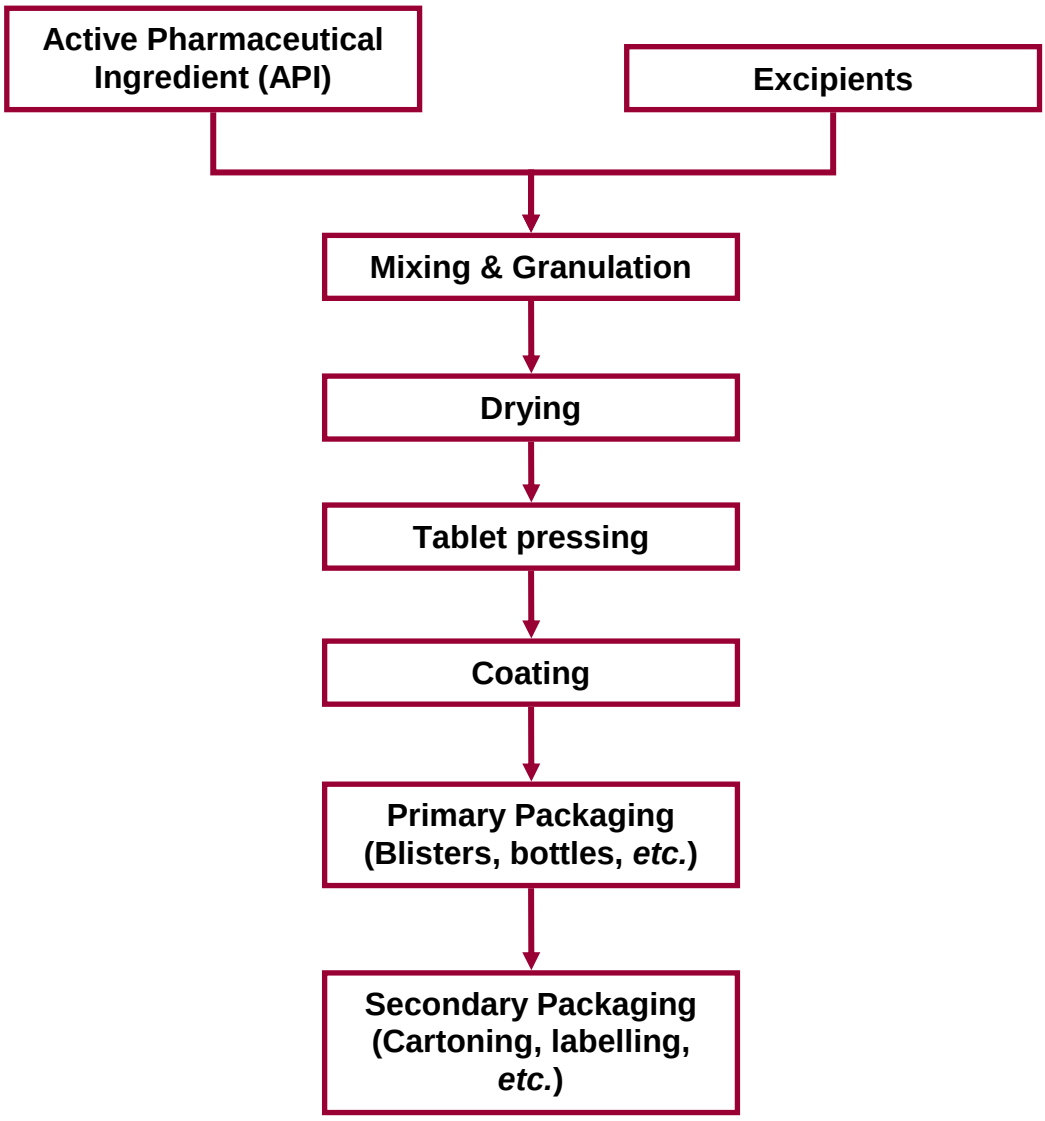
This would be the most attractive scenario politically from an African perspective. It would require considerable effort and a high level of political will to bring to a successful conclusion. It would also have to be a long-term plan as many of the barriers and challenges (outline above) will need considerable time to overcome (*e.g.* infrastructure development, training of suitably qualified staff). African manufacturers would have the re-assurance needed to invest for the long-term and to raise the standards of their facilities.

The challenge of this scenario is that any preference shown to locally-based manufacturers, especially over quality standards, would likely lead to problems with global funders (*e.g.* Global Fund). These organisations and the governments and organisations that supply them with money will have problems if they are seen to support anything that can be interpreted as "second class drugs for poor people". If higher prices have to be charged for locally sourced drugs (*e.g.* a 10% premium), this may conflict with the value for money requirements of the Global Fund and other organisations. A key argument that will need to be answered is whether it is proper to use health-related initiatives funded primarily with international aid money to support primarily economic development goals.

Figures

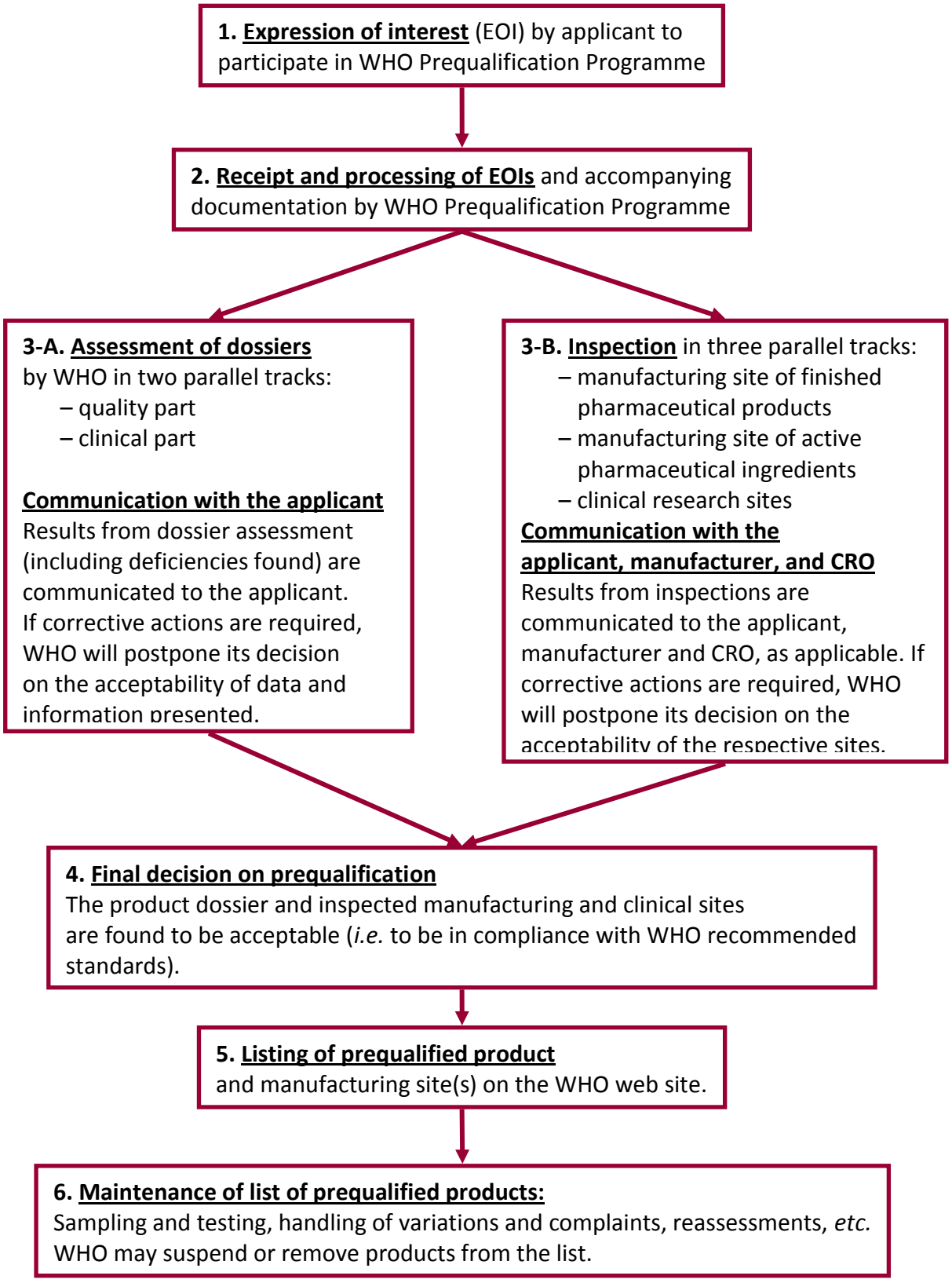
Fig 1: Pharmaceutical Manufacturing Process for Tablets[45]:

This diagram represents the stages in the secondary manufacture of a pharmaceutical product. All Africa-based manufacturers are involved in secondary manufacture and not in primary manufacture of APIs or excipients for antimalarials.



[45] Association of the British Pharmaceutical Industry. [Accessed 2010 10 Dec]. Available from: http://www.abpi.org.uk

Fig 2: Flowchart of WHO Prequalification of Pharmaceutical Products:



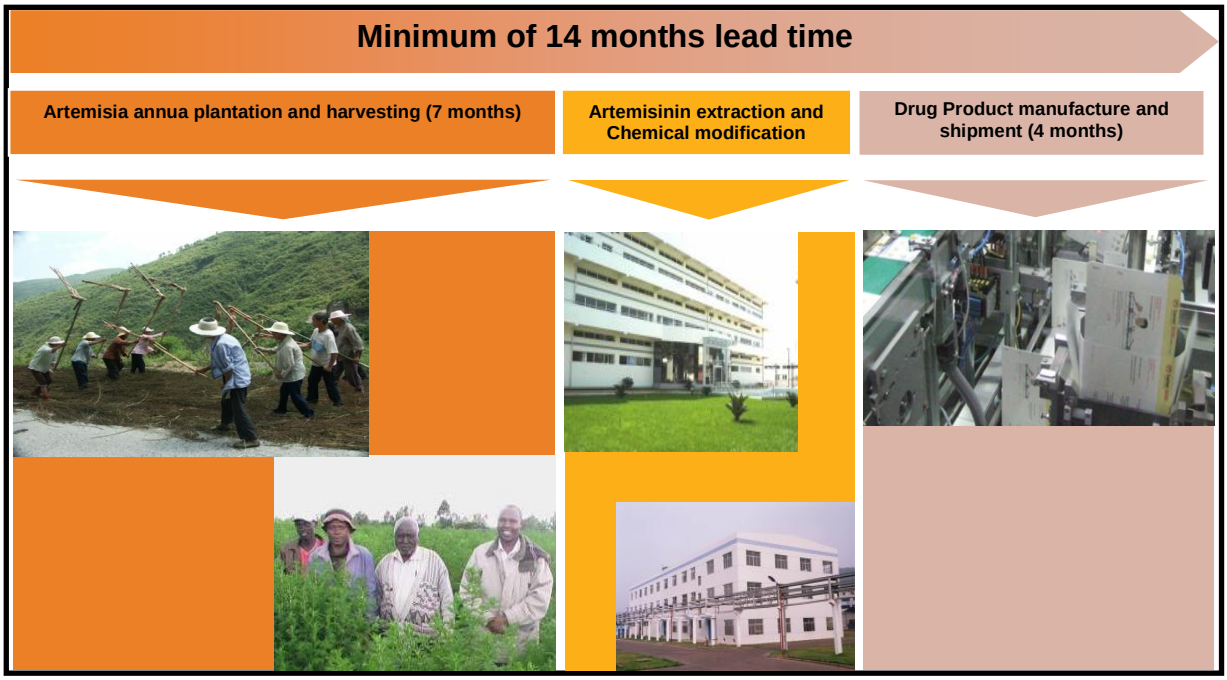
Notes to Fig 2[46]:

1. WHO-PQ follow-up inspections are scheduled in accordance with an SOP on a risk basis, taking into account various factors such as the type of products manufactured, activities performed on site, history of compliance, quality systems of the site and product risk. Inspections could thus be done on an annual basis or every two, 3 or 4 years for APIs or FPPs. A follow-up inspection is performed within 6 months after the initial inspection where corrective actions taken by the manufacturer will be verified.
2. The WHO-PQ Programme publishes World Health Organization Public Inspection Reports (also known as a WHOPIR). A WHOPIR is a summary of the inspection report and reflects the inspection performed and gives a summary of the areas covered during an inspection. It excludes confidential and proprietary information. The WHOPIR is prepared only when all non-compliances with WHO norms and standards such as GMP/GCP or other equivalent guidelines have been satisfactorily corrected by the manufacturers or organizations. The WHOPIR is valid for a maximum of 3 years, unless the site is found to be non-compliant in another inspection before the 3 years lapsed.

[46] World Health Organisation. Prequalification – Inspections. Geneva: WHO; [updated 2009 15 Jul: accessed 2011 03 Feb]. Available from: http://apps.who.int/prequal/info_general/documents/inspection/Q-A.pdf

Fig 3: Coartem® Production Cycle:

This is a typical production cycle for an ACT, showing how the length of the growing season for *Artemisia annua* and the extraction and chemical modification times make the overall production cycle very long and hence increase uncertainty in defining the supply-and-demand relationship.[47]



[47] Reproduced with permission from Novartis Pharma.

Fig 4: Coartem® Packaging

This is one of the best known examples of an antimalarial with packaging designed specifically to improve communication about how to use the product properly.[48]

[48] Reproduced with permission from Novartis Pharma.

Annexes

Annex 1: List of Abbreviations

ACT	Artemisinin-containing Combination Treatment
ALMA	African Leaders' Malaria Alliance
AMC	Advanced Market Commitment
AMFm	Affordable Medicines Facility - malaria
API	Active Pharmaceutical Ingredient
CHMP	Committee for Medicinal Products for Human Use
CRO	Clinical Research Organisation
EMeA	European Medicines Agency
EOI	Expression of Interest
ERP	Expert Review Panel
EU	European Union
FDA	Food & Drug Administration
FDC	Fixed Dose Combination
FPP	Finished Pharmaceutical Product
GCP	Good Clinical Practice
Global Fund	Global Fund to fight AIDS, Tuberculosis, and Malaria
GMP	Good Manufacturing Practice
LIC	Low Income Country
MMV	Medicines for Malaria Venture
NDRA	National Drug Regulatory Authority
PMI	President's Malaria Initiative
QA	Quality Assurance
QC	Quality Control
RBM	Roll Back Malaria Partnership
SRA	Stringent Regulatory Authority
UNAIDS	Joint UN Programme on HIV/AIDS
UNIDO	United Nations Industrial Development Organisation
WHO	World Health Organisation
WHO GMP	WHO Global Malaria Programme
WHO-PQ	United Nations Pre-Qualification Programme (managed by WHO)

Annex 2: List of Definitions[49, 50]

Active Pharmaceutical Ingredient (API)	A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a therapeutically active compound (ingredient).
Advanced Market Commitment	A commitment by governments and funding bodies to commit money to buy drugs or vaccines (usually still in development) at a pre-agreed price to support the development of new products.[51]
Bioequivalence	Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of availability), after administration in the same molar dose, are similar to such a degree that their effects can be expected to be essentially the same.
Excipient	Any component of a finished dosage form other than the claimed therapeutic ingredient or ingredients.
Finished Pharmaceutical Product (FPP)	A medicine presented in its finished dosage form that has undergone all stages of production, including packaging in its final container and labelling.
Fixed Dose Combination (FDC)	A combination of two or more active pharmaceutical ingredients in a fixed ratio of doses.
Interchangeability	An interchangeable pharmaceutical product is one that is therapeutically equivalent to a comparator (reference) product.
Multisourced Product	Multisource pharmaceutical products are pharmaceutically equivalent products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.
Pharmaceutical Equivalence	Products are pharmaceutical equivalents if they contain the same amount of the same active substance(s) in the same dosage form; if they meet the same or comparable standards; and if they are intended to be administered by the same route. Pharmaceutical equivalence does not necessarily imply therapeutic equivalence, as differences in the excipients and/or the manufacturing process can lead to differences in product performance.
Product Formulation	An active pharmaceutical ingredient (or combination of ingredients), dosage form, and strength. Note: different FPPs may exist for the same Product Formulation.

[49] Global Fund to fight AIDS, TB, & Malaria. Global Fund Quality Assurance Policy for Pharmaceutical Products. Geneva: Global Fund; 2009 [accessed 2011 06 Jan]. Available from: http://www.theglobalfund.org/documents/psm/Annex1-%20FullTextRevisedQualityAssurancePolicy_en.pdf

[50] World Health Organisation. Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products: A Manual for Drug Regulatory Authorities. Geneva: WHO; 1998. WHO/DMP/RGS/98.5. Glossary; p. 33. [accessed 2011 06 Jan]. Available from: http://apps.who.int/prequal/default.htm

[51] What is an AMC? GAVI Alliance [accessed 2011 03 Feb]. Available from: http://www.vaccineamc.org/about.html

Therapeutic Equivalence	Two pharmaceutical products are therapeutically equivalent if they are pharmaceutically equivalent and, after administration in the same molar dose, their effects with respect to both efficacy and safety are essentially the same, as determined from appropriate bioequivalence, pharmacodynamic, clinical or in vitro studies.

Annex 3: Antimalarials Contained in 8th Invitation to Submit an Expression of Interest (EOI)

The medicinal products listed below are those included in the 8th Invitation (August 2009) and are those that have been identified by the WHO Global Malaria Programme (WHO GMP) as vital to the effective treatment for people living with malaria. These lists are updated regularly as the needs and availability of antimalarial medicinal products change.

1. Artemisinin-based fixed dose oral combination formulations

- Artemether + Lumefantrine,
    - tablet 20 mg + 120 mg;
    - tablet 40 mg + 240 mg
    - tablet 60 mg + 360 mg;
    - tablet 80 mg + 480 mg
- Artesunate + Amodiaquine,
    - tablet 25 mg + 67.5 mg;
    - tablet 50 mg + 135 mg;
    - tablet 100 mg + 270 mg
- Artesunate + Amodiaquine,
    - tablet 25 mg + 76.5 mg;
    - tablet 50 mg + 153 mg;
    - tablet 100 mg + 306 mg
- Dihydroartemisinin + Piperaquine Phosphate,
    - tablet 40 mg + 320 mg;
    - tablet 20 mg + 160 mg;

2. Artemisinin-based fixed dose combination or co-blistered oral formulations

- Artesunate + Mefloquine,
    - tablet 25 mg + 125 mg;
    - tablet 50 mg + 250 mg;
    - tablet 100 mg + 250 mg
- Artesunate + Sulfadoxine + Pyrimethamine,
    - tablet 25 mg + 250 mg + 12.5 mg
    - tablet 50 mg + 500 mg + 25 mg;
    - tablet 100 mg + 500 mg + 25 mg

3. Artemisinin-based fixed dose combination or co-blistered oral paediatric formulations, preferably dispersible

- Artemether + Lumefantrine
- Artesunate + Amodiaquine
- Artesunate + Mefloquine
- Artesunate + Sulfadoxine + Pyrimethamine

4. Artemisinin-based single-ingredient formulations

- Artemether, oily injection 20 mg/ml; 40 mg/ml; 80 mg/ml
- Artesunate, powder for injection 60 mg (vial)
- Artesunate, suppositories 50 mg; 100 mg; 200 mg; 400 mg
- Artesunate, tablet* 25 mg; 50 mg; 100 mg

5. Other antimalarial medicines

- Mefloquine, tablet 250 mg
- Sulfadoxine + Pyrimethamine, tablet 500 mg + 25 mg