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PHARMACEUTICAL MANUFACTURING PLAN FOR AFRICA

Business Plan



*Prepared as part of the AUC-UNIDO
Partnership*

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Addis Ababa, 2012

ACKNOWLEDGEMENT

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FOREWORD

During the last decade promoting sustainable access to quality and affordable medicines and integrating local production as part of the overall health systems strengthening package has been of significant concern to African leaders.

A viable pharmaceutical industry in Africa shall not only impact on the African health system and its capacity to respond to the health needs of the people but also will contribute to the overall socioeconomic development of the continent.

For this reason, African governments have committed to enhancing the attainment of one of the set targets of the 8th Millennium Development Goal, to increase the proportion of the population with access to affordable essential drugs on a sustainable basis.

The African Union Commission has been at the forefront in galvanizing the necessary political will and providing the leadership to the broad range of processes required for promoting a sustainable local pharmaceutical industry.

The Commission has made significant efforts towards ensuring delivery on set objectives of Africa's highest decision making body (The Assembly of Heads of State and Government) as they relate to the implementation of a Pharmaceutical Manufacturing Plan for Africa (PMPA). These range from conducting studies to establish Africa's local pharma production capacity, building strategic partnerships required for the development of a concrete action plan, to engaging governments in the development of the Business Plan for the operationalization of the PMPA.

This Business Plan is a product of multi-stakeholder efforts all geared towards providing a package of solutions to address the various challenges confronting the African pharma sector in general. It is not an end in itself but rather a means through which governments either through their national systems or regional economic communities will engage with relevant partners to implement specific activities according to their unique needs/priorities.

The road ahead remains long and challenging but the desired objectives remain compelling and non-negotiable. Consequently I invite all stakeholders from member state governments to Regional Economic Communities; from the Private for Profit Sector to Donors and Development partners to strategically engage and collaborate, creating the unity of purpose and necessary synergies to realize the noble objectives of this Business Plan.

Bience P. Gawanas

Commissioner for Social Affairs

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LIST OF ABBREVIATIONS

AA	artesunate/amodiaquine
ACT	Artemisinin-based Combination Therapy
AfDB	African Development Bank
AL	artemether/lumefantrine
ALMA	African Leaders Malaria Alliance
AMFm	Affordable Medicines Facility for malaria
AMRH	African Medicines Regulatory Harmonization
ANDA	Abbreviated New Drug Application
ANDI	African Network for Drugs and Diagnostics Innovation
API	Active Pharmaceutical Ingredient
ARIPO	Africa Regional Intellectual Property Organization
ARV	antiretroviral drug
BA/BE	Bioavailability/Bioequivalence
AU	African Union
AUC	African Union Commission
BRIC	Brazil, Russia, India and China
CCATP	Collaborating Centre for Advocacy and Training in Pharmacovigilance
CHAI	Clinton Health Access Initiative
CL	Compulsory Licence
CMS	Central Medical Store
COHRED	Council on Health Research for Development
CSIR	Council for Scientific and Industrial Research (RSA)
CTD	Common Technical Document
DE	Data Exclusivity
DFI	Development Finance Institution
DFID	Department for International Development (UK)
DNDi	Drugs for Neglected Diseases Initiative
DRC	Democratic Republic of Congo
EAC	East African Community
ECCAS	Economic Community of Central African States
ECOWAS	Economic Community of West African States
EDL	Essential Drugs List
EGA	European Generic Medicines Association
EIU	Economist Intelligence Unit
EMA	European Medicines Agency
EML	Essential Medicines List
FDA	Food and Drug Administration (U.S.)
FDC	Fixed Dose Combination
FEAPM	Federation of East African Pharmaceutical Manufacturers
FKPM	Federation of Kenyan Pharmaceutical Manufacturers
GDP	Good Distribution Practice
GIZ	Deutsche Gesellschaft fuer Internationale Zusammenarbeit
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GWP	Good Warehousing Practice
GPO	Government Pharmaceutical Organization (Thailand)
HAI	Health Action International
HAT	Human African Trypanosomiasis

ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMA	Indian Drug Manufacturers' Association
IFC	International Finance Corporation
IFHA	Investment Fund for Health in Africa
IPA	Indian Pharmaceutical Association
IPO	Initial Public Offering
HR	Human Resource
ICT	Information and Communications Technology
KEMRI	Kenya Medical Research Institute
KETAM	Kenya chapter of the Pan African Treatment Access Movement
KSP	Kilimanjaro School of Pharmacy
LEAP	Leishmaniasis East Africa Platform
LDC	Least Developed Country
LNCPP	Laboratoire National de Contrôle des Produits Pharmaceutiques (Algeria)
MASC	Medicines and Allied Substances Control
MDR-TB	multidrug-resistant tuberculosis
M & A	Mergers and Acquisitions
M & E	Monitoring and Evaluation
MCAZ	Medicines Control Authority of Zimbabwe
MCC	Medicines Control Council (RSA)
MeTA	Medicines Transparency Alliance
MMV	Medicines for Malaria Venture
MoF	Ministry of Finance
MoH	Ministry of Health
MRC	South African Medical Research Council
MSF	Medecins sans Frontieres
MUHAS	Muhimbili University of Health and Allied Sciences (Tanzania)
NAFDAC	National Agency for Food and Drug Administration and Control (Nigeria)
NEPAD	New Partnership for Africa's Development
NGO	Non-Governmental Organisation
NIPER	National Institute of Pharmaceutical Education and Research
NMRA	National Medicines Regulatory Authority
NRF	National Research Foundation (RSA)
OECD	Organisation for Economic Co-operation and Development
PDP	Product Development Partnership
PE	Private Equity
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PMAG	Pharmaceutical Manufacturers Association of Ghana
PMI	Presidents's Malaria Initiative (U.S.)
PMPA	Pharmaceutical Manufacturing Plan for Africa
PPP	Public Private Partnership
QC	Quality Control
QMS	Quality Management System
R & D	Research and Development
REC	Regional Economic Community
RoK	Republic of Korea
RSA	Republic of South Africa
SADC	Southern African Development Community
SAGMA	Southern African Generic Medicines Association
SARPAM	Southern African Regional Programme on Access to Medicines and Diagnostics

SEZ	Special Economic Zone
SLF	Saint Luke Foundation (Tanzania)
SMZ	Sulfamethoxazole
SPC	Supplementary Protection Certificate
SRA	Stringent National Medicines Regulatory Authority
SSA	sub-Saharan Africa
TA	Technical Assistance
ToR	Terms of Reference
TPI	Tanzanian Pharmaceutical Industries
TPM	Total Productive Maintenance
TPS	Toyota Production System
TRIPS	Trade and Related Aspects of Intellectual Property Rights
UK	United Kingdom
US	United States of America
USP	U.S. Pharmacopeial Convention
XDR-TB	extensively drug-resistant tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNCTAD	United Nations Conference on Trade and Development
UNDP	United Nations Development Programme
UNICEF	United Nations Children's Fund
UNIDO	United Nations Industrial Development Organization
VC	Venture Capital
WAHO	West African Health Organisation
WAPMA	West African Pharmaceutical Manufacturers Association
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WTO	World Trade Organization

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EXECUTIVE SUMMARY

This Business Plan addresses a complex industry and covers a diverse range of contexts across our 54 member states. Strengthening our ability to produce high quality, affordable pharmaceuticals across all essential medicines will contribute to improved health outcomes and the realization of direct and indirect economic benefits. This is the vision of the Pharmaceutical Manufacturing Plan for Africa (PMPA) endorsed by our Heads of State and Government at the summit in Accra in 2007. This Business Plan outlines a recommended approach for achieving these aims. It is designed to benefit all our member states through contributing to improved access to affordable, safe and efficacious essential medicines.

In Africa, we bear a disproportionate burden of disease with, for example, 75% of the world's HIV/AIDS cases and 90% of the deaths due to malaria. Our people suffer more than most from tuberculosis and there are many other infectious diseases that cause substantial morbidity and mortality. The extreme impact of infectious diseases is largely felt in sub-Saharan Africa (SSA) as our countries in the North have disease profiles that are more closely related to those of industrialized countries, with cardiovascular disease, diabetes and cancer being public health priorities. Non-communicable diseases are also becoming increasingly prominent across the rest of the continent given the demographic changes that are taking place and they are predicted to overtake infectious diseases as the leading causes of death in Africa by 2030.

These forecasts reflect the changing lifestyles that are associated with economic prosperity, a future that is predicted for much of our continent over the coming years. The future will also likely see a reduction in the level of donations in support of our healthcare systems as the global financial crisis plays out. Therefore, it is imperative that we implement a plan for developing our industry so that we can ensure access to quality affordable medicines independent of donations. Furthermore, there is the need to improve the quality of products to which our people are exposed across the Essential Medicines List (EML) as evidence suggests that there is significant penetration of sub-standard and counterfeit products in our markets.

The 4th Conference of African Ministers of Health directed the African Union Commission (AUC) to develop a Business Plan for the operationalization of the PMPA, a directive that was further re-emphasised at the 5th meeting in Namibia in 2011. The AUC duly convened a stakeholders meeting in Chad to review terms of reference which have guided the development of this Plan. That meeting reconfirmed that the objectives of the Business Plan should be to develop a sustainable supply of affordable, quality essential medicines; to improve public health outcomes; and to contribute to industrial and economic growth.

This Business Plan is premised on the belief that industrial development of the pharmaceutical sector will contribute to improved public health outcomes, provided that the development of the industry is based on the principle that all manufacturers supplying pharmaceuticals to our people should ultimately meet international standards of production. However, it is also recognized that we need to be pragmatic and that change cannot happen overnight. In view of this, we propose a road map approach where the industry is both supported and required to reach international standards of production over a period of time. Furthermore, the impact of 'sub-standard' production will be mitigated through ensuring that critical products that would have serious public health consequences should they be of unsatisfactory quality are only manufactured by those of our companies that have reached certain requisite standards.

The context in which pharmaceutical manufacturing takes place is determined by a number of actors who form the 'pharmaceutical manufacturing system'. These entities include the manufacturers themselves, national medicines regulatory authorities (NMRAs), various government ministries, trade associations and an array of distribution channels. Other key players include institutions that develop the human capital for this knowledge intensive sector.

Moreover, given the capital intensive nature of the pharmaceutical industry, manufacturers need to access investment. An appetite from various different sources of investment capital for the sector is essential if companies are to be able to make the significant investments required to reach and maintain international standards.

The combined impact of these different actors determines the ability and desire of companies to manufacture products to international standards and the degree to which such manufacturing can be sustainable. The regulator should play a key role in ensuring that products are manufactured according to Good Manufacturing Practices (GMP). It should also oversee the distribution of products to ensure adherence to Good Distribution Practices (GDP) and Good Warehousing Practices (GWP), as well as oversee the market place through pharmaco-vigilance and post marketing surveillance. Various government ministries have policy tools at their disposal that can be used to support the development and sustainability of the industry sector in a country.

The level of development of the manufacturing system in our countries varies dramatically. The number of companies that are registered ranges from over 200 in Nigeria to none in a number of our countries. In total, it is estimated that some form of manufacturing takes place in 38 countries. There is wide divergence in the level of regulatory oversight, with the Republic of South Africa (RSA) and countries such as Algeria and Tunisia in the North having strong institutions. A World Health Organization (WHO) survey of 26 of our countries found that many regulatory authorities lacked the capacity to fulfil the basic functions required for the satisfactory protection of public health. Given this limited capacity, it is impossible for many of our regulators to oversee the supply of products from a thousand plus companies spread across different continents. In view of this, the proximity of high quality production through developing our industries in situ is a means by which our resource-constrained regulators can establish secure sources of supply.

In other developing countries, such as China and India where there are flourishing pharmaceutical sectors, the industry is reputed to benefit from a number of policy measures including protection through tariff regimes and procurement preferences as well as direct support such as interest subsidies, export credits, cheap utilities, working capital credits and tax holidays. Consequently, imports into our continent have often been subsidized through significant support from their respective governments. Furthermore, they often enjoy zero tariffs when they come into our countries.

Conversely, in some of our nations, domestic manufacturers have to pay up to 25% duty on imported raw materials. Therefore, whilst a number of Ministries of Health and/or NMRAs have, for example, identified strengthening the local manufacturing sector as an important objective, there is often policy incoherence across government ministries. This creates an overall environment that is not conducive to the development of our pharmaceutical industries.

There is very limited manufacturing of Active Pharmaceutical Ingredients (APIs) in Africa (limited exceptions being RSA, Egypt and Ghana) and most of our companies are involved in final formulation and packaging of drugs. The quality standards to which our manufacturers adhere vary significantly between countries and within countries. As mentioned, RSA and most North African countries have strong, well developed industries. We have examples of companies across our continent that have reached or are striving for international standards. We have others that have the ambition to do so but who have, as yet, not been able to access the detailed technical know-how or the investment needed to progress towards this mark. There are other entities that are happy to continue with the current status quo given that they operate with a relatively low cost base and there is limited political power or capacity for NMRAs to take action against them.

The industry does face serious challenges if it is to achieve and maintain the standards that should be required. These challenges include limited access to finance; limited availability of skilled human resources; inability to access the detailed know-how necessary to implement an upgrading programme or design a new plant; significant costs involved in the proper development of new products; the aforementioned policy incoherence; and underdeveloped supporting industries.

The perspective of individual manufacturers is somewhat dependent on where they stand in terms of ambition and progress towards improved quality standards. A major factor hampering achievement of the overarching goal of universal high quality production is insufficient regulatory oversight. Such oversight is a key factor since lack of it can result in sub-standard products (both domestically produced and imported) and counterfeit products taking market share from domestic firms genuinely aspiring to high quality production. This has knock-on effects and it is, for example, one of the issues that investors cite as limiting their appetite for the sector.

In addition to the challenges faced by the industry, there are underutilized opportunities to assist and promote the development of pharmaceutical manufacturing on our continent and for it to contribute to improved public health outcomes. For example, the Trade Related Aspects of Intellectual Property Rights (TRIPS) flexibilities have generally not been utilized; there are limited links between industry and academia; and collaboration between companies in Africa, as well as with international manufacturers, is quite rare. In most countries, the range of products is limited to a small proportion of those required by a fully functioning health system. These underutilized opportunities offer substantial potential benefits, including expansion of the current range of locally manufactured products.

Given the diverse range of contexts and the array of aspects that need to be addressed to a greater or lesser extent in each country, this Business Plan proposes an approach where a generic package of solutions is developed. This can then be tailored to the specific needs of each of our countries. The solutions package includes guidance on incentives in support of the sector; a Good Manufacturing Practice (GMP) road map and associated risk assessment of WHO's Essential Medicines List (EML); a syllabus for developing the human resources required for the long term sustainability of the industry; various mechanisms for accessing know-how in the short term, including a Partnership and Business Linkages Platform (that would also assist companies to, for example, establish relationships with local, regional and international players in order to increase product ranges, mobilize investment, etc.); and includes technical assistance to enable regulators to devise and implement organizational development plans. It also proposes a process by which the different stakeholders in a country can come together to develop a shared strategy for the sector and a means by which this strategy can be implemented.

Key to the sustainability of manufacturing on the continent is the degree to which our manufacturers can compete with imports. As pointed out, remedying the policy incoherence will go some way to improving competitiveness and achieving efficient production by using modern production management techniques has the potential to increase capacity utilization of plants. Evidence suggests that our companies can compete with, for example, schedule M compliant manufacturers in India whilst still operating according to international GMP. Therefore, another key part of the solutions is assisting companies to embrace such approaches and constantly look to improve the efficiency with which they produce.

As well as the generic solutions package for implementation at country level, we will undertake activities at the regional and continent wide levels, such as lobbying for an extension to the TRIPS flexibilities beyond 2016. Also, upon request, we will assist Regional Economic Communities (RECs) to develop strategies and will work with centres of excellence to develop novel formulations for dissemination to companies that have reached international GMP standards. There is also the need for further deliberation on issues such as traditional medicines, expanded manufacturing of APIs on the continent, and the need for improved supply of blood products. Recommendations on such issues will be developed in the course of implementing the Business Plan (e.g. WHO is proposing to conduct a feasibility study into blood products in Africa, the findings of which could be incorporated into the PMPA in the future).

This Business Plan puts forward a comprehensive package of solutions for the development of pharmaceutical manufacturing on our continent. The broad range of disciplines that need to be covered and the expertise required mean that no one entity can deliver all the necessary aspects and a range of organizations will need to collaborate to fulfil the ambition. An important issue to be addressed is the fragmentation of our markets and work under the African Medicines Regulatory Harmonization initiative (AMRH) is well advanced. It will be critical that the broader work under this Business Plan is coordinated closely with the AMRH work in order to advance towards the objectives set by the PMPA.

As well as collaboration with AMRH, we propose to establish a consortium of key partners who will assist us in this undertaking. Initial discussions have taken place with various African and international bodies that could come together to cover the full range of interventions required. Under the implementation approach for this Business Plan, a key first step will be to establish the legal basis for the consortium and to develop the chemistry between the different actors so that genuine progress can be made. We have invited the United Nations Industrial Development Organization (UNIDO) to assist us in setting up the consortium and to play a coordinating role as we move forward. In addition to establishing the consortium, we will need to mobilize significant resources for the implementation of this Business Plan. A detailed budget will be prepared once the consortium has designed a shared action plan. However, an indicative budget has been prepared and it is estimated that implementation will cost US\$ 54mn over a five year period.

Other activities during the early stages of implementation will include further refinement of the generic solutions package and inviting expressions of interest from member states who wish to engage with the African Union Commission (AUC) for the development of their industry or of their regulatory systems. This would enable those states to realize public health gains from access to regional sources of high quality medicines. During a scale up phase, agents acting on behalf of the PMPA will work with national level stakeholders to develop strategies to achieve their shared ambitions. Once defined, these ambitions will be translated into a detailed action plan based on the expertise within the consortium which will also assist in national level implementation.

This Business Plan does not represent a source of funding for public or private sector players but is a package of technical assistance which countries can access. Initial discussions with the World Bank have suggested that there could be interest in supporting investment in, for example, National Medicines Regulatory Authorities (NMRAs) although ultimately it will be the responsibility of individual countries to finance the recommended investments (whether in terms of bricks and mortar or through support to the industry in the form of incentives).

The nature of the manufacturing industry and the complexity of the system within which it operates mean that it will take time for the full benefits to be realized. There will also be the need for coordination of many different actors at the country level and at the international community level. In view of this, a prerequisite for the success of this Business Plan is the ongoing political will at the highest level to bring parties into alignment and to enable sustainable progress to be made. Only then will the vision of increasing access to essential medicines for our people, through a strengthened African pharmaceutical industry, become reality.

SWOT ANALYSIS

This Business Plan puts forward a detailed approach to strengthening pharmaceutical manufacturing in Africa in order to improve public health outcomes and to contribute to economic development of our continent. Public health will benefit from improved security of supply and robust regulatory oversight (feasible due to proximity of production) as well as providing a basis from which novel formulations and new products can be developed to tackle specific diseases and treatment challenges that are to be found on our continent. As the global financial crisis continues to evolve, the development of the sector will provide a basis for sustainable treatment programmes as the contribution that donors can make plateaus or even begins to diminish. The sector can also make a contribution to economic growth through enhanced exports, increased intra-African trade, emergence of supportive industries and the reduced reliance on imports that use up precious hard currency and for which only limited regulatory oversight by our national regulatory authorities is possible.

The situation across our countries varies dramatically, however general themes apply to a greater or lesser extent. The following chart summarizes the top line strengths, weaknesses, opportunities and threats that are pertinent to the sector’s ability to contribute to progress across public health and economic development dimensions.

<i>Strengths</i>	<i>Weaknesses</i>
<ul style="list-style-type: none"> • Heightened political interest (and will) to support the local production of medicines. • Demonstrated that high quality production of essential medicines is feasible across our continent. • Strengthening of legal/regulatory framework (off a weak base). • Existence of scientific and technical institutions with the relevant skills in a number of countries (as yet underutilized). • Increasing political stability and rapid economic development provide a strong basis for development of the industry. • Developments in health insurance schemes and health systems with increasing investment in public health. • Some countries have well established pharmaceutical sectors and regulatory institutions that are relatively strong. • Comparatively low labour costs, especially as Indian labour costs begin to escalate. • Some countries already exporting to industrialized markets. 	<ul style="list-style-type: none"> • Level of regulatory oversight varies but in general it is insufficient to protect our citizens and to allow fair competition in our pharmaceutical markets. • Currently heavily dependent on imports which often benefit from export incentives as well as favorable duties and tariffs when compared to domestically manufactured products. • Policy incoherence and absent sector development strategies lead to an environment that is not conducive for the industry to flourish. • High utility costs and unreliable supply. • Limited availability of affordable finance of sufficient magnitude and duration constrains the sector's ability to invest in necessary upgrades to achieve established quality standards. • Small domestic markets and fragmented regional markets hamper companies' ability to manufacture efficiently. • Situation varies dramatically, but in for many companies the systems, processes, premises and equipment at plant level are insufficient to assure quality of production.

<i>Strengths</i>	<i>Weaknesses</i>
	<ul style="list-style-type: none"> • Limited supporting industries including local production of inputs such as APIs, packaging and excipients, as well as availability of services to maintain and repair equipment and to conduct necessary trials to attest to suitability of products. • WHO prequalification scheme covers only a limited range of products whilst the quality assurance for most medicines is under the authority of our highly resource constrained NMRAs.
<i>Opportunities</i>	<i>Threats</i>
<ul style="list-style-type: none"> • Awareness of importance of local production amongst international partners and donors, and growing commitment to support this agenda. • Evidence suggests given a conducive environment our manufacturers can compete with imports and produce high quality products. • Time limited support to industry coupled with requirements (and regulatory oversight) to develop provides viable route for building an international standard industry. • Creating more favorable market conditions will encourage investment in the sector. • Development of the sector (and requisite national and regional level legislation) will enable TRIPS flexibilities to be utilized for improved access to key medications. • Increased prevalence of lifestyle diseases can be more comprehensively addressed through enhanced local production and they represent a growing market opportunity. • Training programmes and institutions exist but need to be expanded and scaled up. • More advanced countries can look to export drugs to international markets. • On-going work under the African Medicines Regulatory Harmonization initiative could lead to defragmented markets at the sub-regional level. • Strong interest from international generic industry and therefore the possibility for local companies to form alliances with international players. 	<ul style="list-style-type: none"> • Without a holistic and robust approach to developing the sector efforts from committed manufacturers will be undermined by on-going penetration of sub-standard and counterfeit medicines. • An on-going lack of evidence as to the prevalence and impact of substandard and counterfeit medications could undermine the long term political will required to develop the industry. • Development of the sector requires coordination across public health and industrial development components otherwise objectives on both fronts will not be achieved. • Without concerted action reliance on Asian imports may increase and quality of products may be increasingly suspect. • If donor assistance plateaus a possible increase in sub-standard products for the pandemic diseases could jeopardize the health of patients and lead to accelerated resistance generation against critical products. • Donor initiatives that can inadvertently have detrimental consequences for the African pharmaceutical industry.

INDICATIVE ACTIVITIES THAT COULD BE CONDUCTED DURING THE IMPLEMENTATION OF THIS BUSINESS PLAN

<i>Area of work</i>	<i>Timeframe (Yrs.)</i>	<i>Key activities</i>	<i>Key success factors</i>
Setting up the programme	1	<ul style="list-style-type: none"> <input type="checkbox"/> Establish consortium <input type="checkbox"/> Resource mobilization <input type="checkbox"/> Invite countries interested in working with the PMPA to express their interest 	<ul style="list-style-type: none"> <input type="checkbox"/> Genuine collaborative spirit between consortium parties <input type="checkbox"/> All partners involved in detailed design of programme <input type="checkbox"/> Credibility of proposal for donors
Develop the solutions package	1	<ul style="list-style-type: none"> <input type="checkbox"/> Design a generic GMP road map <input type="checkbox"/> Conduct risk assessment of the Essential Medicines List <input type="checkbox"/> Develop the HR development package 	<ul style="list-style-type: none"> <input type="checkbox"/> Collaboration between parties (particularly in HR development) <input type="checkbox"/> Addressing complex technical issues (e.g. EML risk assessment) in a pragmatic but scientifically sound way
Establish PMPA field representatives	1	<ul style="list-style-type: none"> <input type="checkbox"/> Appoint regional coordinators to oversee the country level design and implementation of strategies <input type="checkbox"/> Subject to invitations from individual member states, recruit national experts to coordinate strategy design and implementation 	<ul style="list-style-type: none"> <input type="checkbox"/> Government political will <input type="checkbox"/> Initial seed funding for PMPA mobilized
Human Resource Development	1 -> 5	<ul style="list-style-type: none"> <input type="checkbox"/> Develop training programmes <input type="checkbox"/> Offer training <ul style="list-style-type: none"> – Regulatory affairs – Pharmaceutical business management – Pharmaceutical manufacturing – Plant operations & maintenance <input type="checkbox"/> Facilitate short term access to know how (e.g. business partnerships/ citizens encouraged to return from Diaspora) 	<ul style="list-style-type: none"> <input type="checkbox"/> Easy access to visas and work permits for expatriate staff and PMPA team of experts <input type="checkbox"/> Collaboration with Stringent Regulatory Authorities, ICH, PICGS <input type="checkbox"/> Industry-academia-research institutes interface & partnerships <input type="checkbox"/> Overall credibility of country commitment stimulates interest from partners and encourages citizens to return
Advise governments on design and implementation of a holistic strategy for building sustainable industry and/or benefiting from regional sources of high quality medicines	1-3	<ul style="list-style-type: none"> <input type="checkbox"/> Conduct extensive consultations with industry and all relevant key stakeholders <input type="checkbox"/> Initial strategy submitted for consideration by stakeholder round table process <input type="checkbox"/> Implementation utilizing the expertise within the consortium as described in the “solutions package” tailored to the specific national context 	<ul style="list-style-type: none"> <input type="checkbox"/> Full participation by all stakeholders <input type="checkbox"/> Ongoing political support and buy-in <input type="checkbox"/> Commitment by member states through the appointment of ministry liaison officers

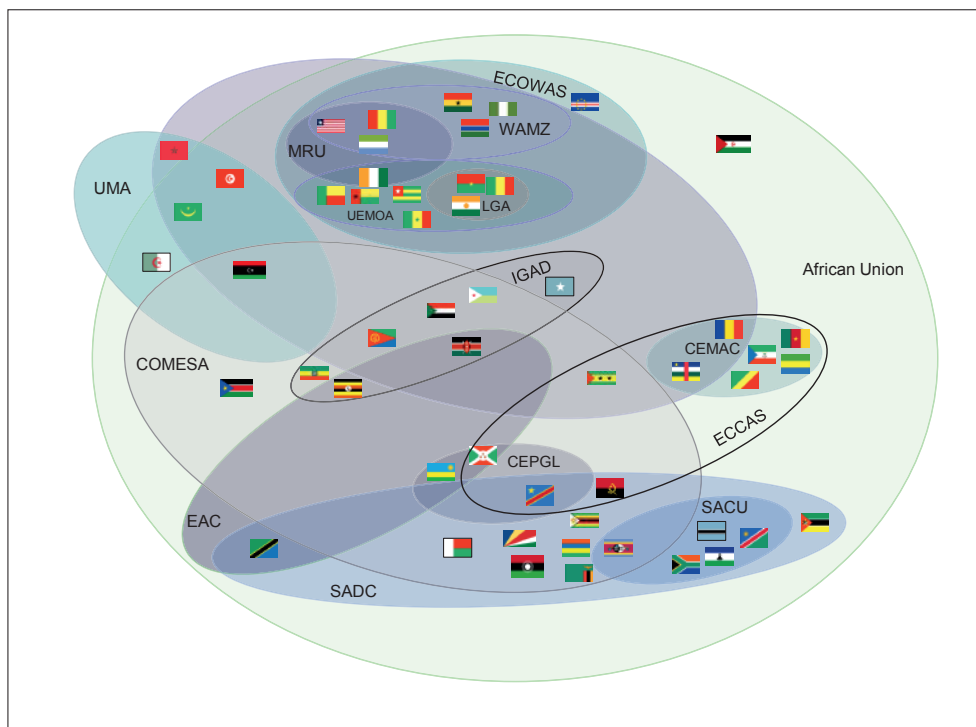
Area of work	Timeframe (Yrs.)	Key activities	Key success factors
Assistance with regulatory systems strengthening & building regulatory capacity at country level	1->5	<ul style="list-style-type: none"> <input type="checkbox"/> TA to NMRAs on optimum organizational structure & development <input type="checkbox"/> Support AMRH work on regulatory harmonization 	<ul style="list-style-type: none"> <input type="checkbox"/> Political support <input type="checkbox"/> Regulator autonomy <input type="checkbox"/> Regulator well-resourced
Assistance to leading companies to achieve stringent regulatory approval	2-3	<ul style="list-style-type: none"> <input type="checkbox"/> Subject to criteria established by the TA, identify leading companies in achieving pre-qualification of products <input type="checkbox"/> Identify individual requirements and set up appropriate technical assistance programmes 	<ul style="list-style-type: none"> <input type="checkbox"/> Companies will need to take advantage of the assistance (which will mainly be in kind) <input type="checkbox"/> Sustainability of such companies will also depend on other aspects of the Business Plan such as specific government support in the short term
Facilitate and promote access to products and technology for international GMP compliant local manufacturers	2-5	<ul style="list-style-type: none"> <input type="checkbox"/> Working with centres of excellence and partners, accelerate research into new product and formulation development, select products for development based on EML <input type="checkbox"/> Diffuse process & other technology to leading companies 	<ul style="list-style-type: none"> <input type="checkbox"/> Access to expertise – ANDI CoE's and American partners <input type="checkbox"/> Ability to get Voluntary Licences or to exploit TRIPS flexibilities <input type="checkbox"/> Tech transfer teams
Facilitate access to affordable finance	2->5	<ul style="list-style-type: none"> <input type="checkbox"/> Through the Partnership and Business Linkages Platform advocate for DFIs such as the African Development Bank & African Export-Import Bank (Afri Exim) to invest in the pharma sector <input type="checkbox"/> As part of holistic approach, advise governments on appropriate initiatives to attract investment into the sector 	<ul style="list-style-type: none"> <input type="checkbox"/> Political leadership <input type="checkbox"/> Partnerships with financial experts <input type="checkbox"/> Government creates a conducive environment for investment
Attaining international quality standards	1->5	<ul style="list-style-type: none"> <input type="checkbox"/> As part of country level implementation of holistic strategy, assist regulators to tailor and execute a GMP Road Map to guide the migration to international GMP standards 	<ul style="list-style-type: none"> <input type="checkbox"/> Incentives and financing available for industry to upgrade <input type="checkbox"/> Regulator has political authority and capacity to enforce requirements
Facilitate partnerships, collaboration and business linkages	1->5	<ul style="list-style-type: none"> <input type="checkbox"/> Establish platforms for facilitating match-making <input type="checkbox"/> Monitor deal flow and advise governments on key considerations for FDI 	<ul style="list-style-type: none"> <input type="checkbox"/> Mutually beneficial relationships can be established <input type="checkbox"/> Platform designed to allow for wide variety of relationships between assorted types of stakeholder

Area of work	Timeframe (Yrs.)	Key activities	Key success factors
Enhancing market data collection	1-5	<input type="checkbox"/> Approach IMS Institute to partner and offer training on market data collection tools <input type="checkbox"/> Implement training	<input type="checkbox"/> Willingness to share data by all stakeholders <input type="checkbox"/> IMS sees potential gain from the partnership
Facilitating market access & promoting intra-regional trade	2->5	<input type="checkbox"/> Support as required to AMRH in moving towards regulatory harmonization <input type="checkbox"/> Approach ARIPO, UNDP, UNCTAD re offering TA and support for amending IPR legislation to incorporate TRIPS flexibilities <input type="checkbox"/> Lobby for extension of TRIPS deadline of 07/01/16 <input type="checkbox"/> Approach REC's on harmonization of IPR	<input type="checkbox"/> Political will <input type="checkbox"/> Harmonize registration requirements <input type="checkbox"/> Political will <input type="checkbox"/> Willingness to amend national legislation to incorporate the TRIPS flexibilities <input type="checkbox"/> Companies show interest in exploiting TRIPS
Providing assistance to exploit TRIPS Flexibilities	1->5	<input type="checkbox"/> Identify products for local production <input type="checkbox"/> Mobilize funding and entice entrepreneurs to invest in API production <input type="checkbox"/> Canvas support for local API producer from local formulators	<input type="checkbox"/> Funding <input type="checkbox"/> Production of competitive API (price and quality)
Promoting and catalyzing API Production	1->5	<input type="checkbox"/> Identify partners already engaged in the area and offer support <input type="checkbox"/> Working with identified partners, codify the knowledge base and create a library of plants with medicinal properties	<input type="checkbox"/> Funding <input type="checkbox"/> Research expertise and collaborations <input type="checkbox"/> Partnerships with traditional healers
Providing assistance to accelerate research and development into traditional medicines	1->5	<input type="checkbox"/> Identify partners already engaged in the area and offer support <input type="checkbox"/> Working with identified partners, codify the knowledge base and create a library of plants with medicinal properties	<input type="checkbox"/> Funding <input type="checkbox"/> Research expertise and collaborations <input type="checkbox"/> Partnerships with traditional healers
Escorting the formation and strengthening of pharmaceutical trade associations	1->5	<input type="checkbox"/> Facilitate formation of national and regional trade associations <input type="checkbox"/> Consult with industry stakeholders	<input type="checkbox"/> Extensive consultations with industry and relevant stakeholders <input type="checkbox"/> Industry willingness to participate <input type="checkbox"/> Government and REC level support

1. INTRODUCTION AND BACKGROUND

This Business Plan addresses a complex industry and covers a diverse range of contexts. Our continent is comprised of 54 countries, and has a total population of just over 1 billion people which equates to about 14% of the global population. With the exception of Morocco, all these independent nations are members of the African Union (AU). They are also organized into various sub-groupings, including Regional Economic Communities (RECs) and trading blocs, with overlap and membership of multiple RECs and trading blocs being commonplace. The picture below is a schematic representation of the complexity of the multiple memberships of various African states and of how we are situated in the different regional economic and trading blocs.

Figure 1: Schematic representation of the overlap of RECs and trading blocs on our continent



Compounding the complexity of the RECs and trading blocs, there are substantial variations in disease profiles and pharmaceutical-sector specific issues in North and sub-Saharan Africa (SSA). The SSA region suffers from a high infectious disease burden whilst the North has a profile not dissimilar to that of the developed world, with cancer, diabetes and cardiovascular disease being leading public health priorities. The industry in the North is also generally more developed than in the SSA region.

As well as significant differences between northern and southern Africa, the status of the pharmaceutical industry varies significantly within SSA. For example, the Republic of South Africa (RSA) has a highly developed industry with some level of primary manufacturing. Other member states have emerging industry sectors with companies at different stages of development whilst others have a handful of manufacturers. Some states have no local pharmaceutical manufacturing at all.

The level of regulatory oversight of medicines varies dramatically across our continent. A few member states have strong regulatory authorities; others have institutions in place which, to a greater or lesser extent, fulfil the functions necessary to oversee the pharmaceutical markets; and some have virtually nonexistent regulatory systems. This multiplicity of regulatory environments and widely varying capacities make regulatory harmonization on the continent a massive challenge and continue to hamper access to affordable quality essential medicines. It is against this background that the African Heads of State and Government adopted the Pharmaceutical Manufacturing Plan for Africa (PMPA) in May 2007.

The PMPA was adopted with the explicit aim of contributing to a sustainable supply of quality essential medicines to improve public health and promote industrial and economic development on the continent¹. Broadly speaking then, the objective is to improve the quality of medicines even in countries that are neither involved in nor contemplating local pharmaceutical production. The African Union Commission (AUC) is of the view that, even in such countries, the PMPA will be of benefit in contributing to access and security of supplies of regionally produced high quality medicines. Such high quality regional sources will allow for a speedier response to country needs. Moreover, the proximity of producing countries will enable closer oversight of the quality of products compared with oversight of those derived from numerous plants across different continents. The quality of products available in such countries will also benefit from strengthened supply chains and the development of post marketing surveillance competencies.

1.1 THE STRATEGIC CONTEXT OF AFRICA'S HEALTHCARE CHALLENGES

African healthcare systems face severe challenges which negatively impact on access to affordable quality healthcare and lead to morbidity and mortality from eminently treatable conditions. The challenges are complex and, amongst others, include a disproportionately high infectious disease burden, a growing chronic disease burden, a shortage of the requisite human resources and the necessary infrastructure to deliver healthcare services, as well as significant funding and budgetary constraints.

1.1.1 High infectious disease burden

The International Finance Corporation (IFC)² estimates that Africa accounts for:

- 25% of the global disease burden
- More than 50% of the global deaths of children under five
- 3% of the world's healthcare workers deployed
- Consumes only 1% of global healthcare expenditure

Specifically, Africa accounts for the bulk of the global infectious disease burden with about 75% of the HIV/AIDS pandemic, 90% of the malaria cases and deaths. In addition, nine African countries (excluding North Africa) rank among the 15 countries with the highest

¹ Pharmaceutical Manufacturing Plan for Africa – CAHM_MIN._8(111) 2007

² IFC – The Business of Healthcare in Africa 2007

tuberculosis (TB) burden in the world. The incidence of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) in Africa is one of the highest in the world.³

Furthermore, according to the World Health Organization (WHO), 90% of child deaths in Africa are attributable to neonatal causes, pneumonia, diarrhoea, measles and HIV and AIDS⁴ whilst the major causes of adult mortality are also related to HIV/AIDS, TB and Malaria.

1.1.2 Growing chronic and non communicable disease burden

In addition to the pandemics and other uniquely African infectious diseases, the continent faces a significant and growing non communicable disease burden. These diseases are major public health issues in the North already and are projected to increase dramatically in SSA due to improving social conditions and rapid urbanisation; environmental issues like air pollution; and an increase in the consumption of alcohol and tobacco products. The rise in chronic diseases will also be exacerbated by sedentary lifestyles. It is estimated that by the year 2020 Africa could have⁵:

- 60 million people with hypertension
- 1 million cases of cancer annually
- 18.6 million people with diabetes

Along with the specific conditions mentioned above, there will be an explosion of other cardiovascular conditions, chronic respiratory diseases and neuro-psychiatric conditions. For example, predictions are that by 2030 non-communicable diseases will have surpassed infectious diseases as the leading cause of death in Africa⁶.

1.1.3 The changing economic context and pharmaceutical industry growth

As well as the changing epidemiology of diseases and demographic changes, the Business Plan will be implemented over a period of time when Africa is expected to undergo substantial economic development. Various commentators have predicted that the continent will experience substantial growth and economic development. For example, the World Bank in November 2010⁷ envisioned Africa's prospects thus:

"We conclude that Africa could be on the brink of an economic takeoff, much like China was 30 years ago, and India 20 years ago."

The McKinsey Global Institute also made the following observation:

*"Africa's growth acceleration resulted from more than a resource boom. Arguably more important were government actions to end political conflicts, improve macro-economic conditions, and create better business climates, which enabled growth to accelerate broadly across countries and sectors"*⁸.

³ WHO Global Tuberculosis Report 2011

⁴ WHO Global Tuberculosis Report 2011

⁵ WHO & DFID (UK)

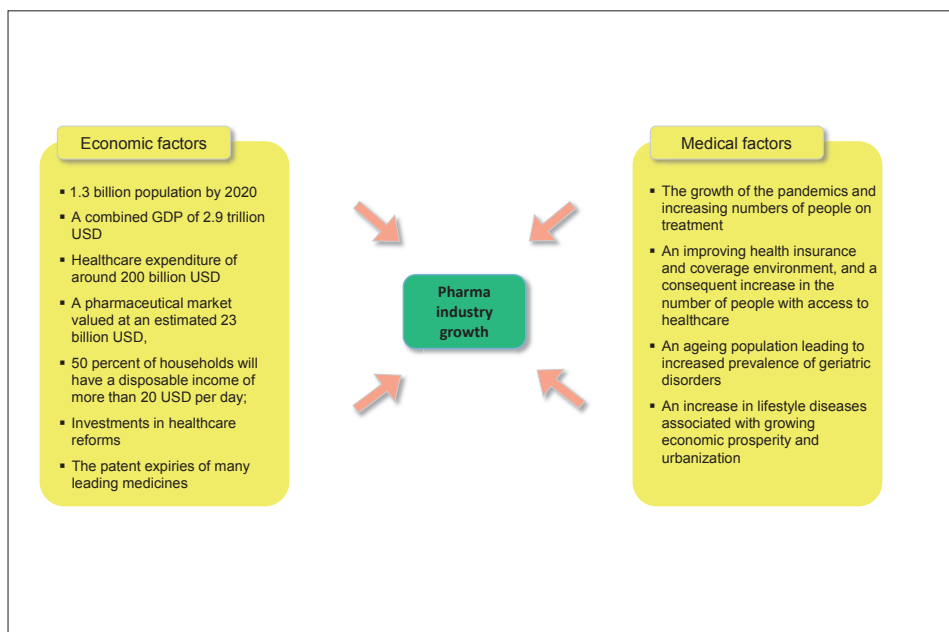
⁶ Colin D Mathers & Dejan Loncar. Projections of Global Mortality and Burden of Disease from 2002-2030. PloS Medicine Nov 2006, Vol. 3, Issue 11

⁷ The World Bank; Africa's future and the World Bank's role in it - http://siteresources.worldbank.org/INTAFRICA/Resources/Africa_s_Future_and_the_World_Bank_s_Role_in_it.pdf

⁸ McKinsey Global Institute – Lions on the Move: The progress and potential of African economies. June 2010

Therefore, the industry, like that of other emerging markets, is expected to grow tremendously in the coming years. The expected growth will largely be driven by economic and medical factors as presented in Figure 2 below. This Business Plan articulates an approach for the PMPA that is designed to catalyse the development of the industry, shorten the time needed for the progressive realization of international quality standards and lead to an increase in product portfolios to address the needs of the continent.

Figure 2: African Pharma Growth Drivers^{9 10},



I.1.4 Shortage of the requisite human resources and infrastructure

The delivery of healthcare requires more than just medicines. There are widespread reports of understaffed health centres and facilities are often not situated where they are most needed. When they are present, they often lack the essential medicines that are needed. It is further estimated that more than a third of the available highly skilled African scientists are now living in the developed world¹¹. A recent survey on the financial cost of doctors emigrating from sub-Saharan Africa revealed that a large number of doctors in sub-Saharan countries were, in fact, working in the United Kingdom, Australia, Canada and the United States. The actual numbers are estimated by various parties to be in the thousands and account for an estimated loss of return on investment for the nine countries of almost US\$2.17bn whilst the net gain for the developed countries to which they emigrated was estimated at US\$4.55bn¹².

This points to the fact that the training capability and talent in the basic and advanced sciences is there. However, a key problem for the continent is the high attrition rate and the brain drain although we also need to increase the output of skilled scientists. It also means that there is a large pool of people who can be tapped to support the continent’s objectives and that, as in the case of India and China, it may be possible to repatriate skills from the Di-

⁹ Africa Progress Report 2010.

¹⁰ McKinsey Global Institute – Lions on the Move: The progress and potential of African economies. June 2010.

¹¹ Joint Statement by the Network of African Science Academies July 2009 - www.nationalacademies.org/includes/NA-SACbraindrain09.pdf (accessed December 2011.)

¹² Edward J. Mills et al. The financial cost of doctors emigrating from sub-Saharan Africa: human capital analysis. British Medical Journal publication. BMJ 2011;343:d7031 doi: 10.1136/bmj.d7031 (published 24 November 2011).

aspora when the environment in Africa becomes conducive to the expression of such skills.

1.1.5 Inadequate distribution infrastructure

The lack of proper infrastructure also contributes to poor health outcomes. For example, there is anecdotal evidence that due to the distribution difficulties caused by insufficient infrastructure in some countries, a percentage of donated drugs expire on shelves in government central medical stores without ever reaching the areas of greatest need in rural clinics and hospitals. Conversely, there is a body of evidence that suggests that locally manufactured products are more readily available in the remote rural parts than imported products^{13, 14}. This is an important development and speaks to the potential impact of assisting the development of local industry.

1.1.6 Chronic healthcare underfunding

African healthcare systems have historically been severely underfunded. Despite the Abuja Declaration in which African Heads of State and Government committed to spending 15% of GDP on healthcare, very few countries have done so and many still grapple with chronic underfunding and very limited healthcare budgets. Inevitably, this funding gap compromises care since the delivery of healthcare in Africa is largely dependent on public sector funding albeit that a few markets have fairly developed private sector healthcare delivery platforms. Even in instances where the public sector is the primary method of health delivery, various sources estimate that out of pocket spending, especially for medicines, is as high as 60% as a result of frequent medicine shortages at public institutions. As a consequence of the funding gap, many donors have come forward and today a large proportion of the health budgets and treatment programmes on the continent are financed or subsidized by international donors.

The over reliance on donor funding, especially for the pandemic conditions, is laden with difficulties especially in the current setting of reducing donor commitments and increasing treatment gaps. Of necessity, this calls into question the sustainability of treatment programmes and healthcare delivery. The Economist Intelligence Unit (EIU) makes this observation:

“By 2022 continued global economic instability will lead to cuts in foreign aid budgets and leave many donor organisations overstretched, with the result that many of them are forced to pull out of African countries. The migration of skilled medical personnel to developed countries is likely to accelerate. The initial consequences of such a development could be empowering for many countries, as well as catastrophic for a smaller number. Countries with greater resources will use the opportunity for emancipation from charity to build up their own local manufacturing capability for basic drugs and medical equipment. In the medium term, booming economies in these more fortunate countries will attract international companies from high-growth markets to develop generic drugs locally, to train local medical staff, to offer new insurance products and to set up research and development centres on the continent”¹⁵.

This view is supportive of similar sentiments raised by various other sources that have spoken of the need for Africa to begin planning and preparing for health provision post the aid boom. Attention is drawn to the urgent need to develop local pharmaceutical production ca-

¹³ Mackintosh M, Mujinja P.G.M. Pricing and competition in essential medicines markets: the supply chain to Tanzania and the role of NGOs - IKD Working Paper No. 32 July 2008.

¹⁴ Mackintosh M. Essential Medicines, supply chain and inequalities - DIME / FINNOV / IKD Workshop INNOVATION AND INEQUALITY: The Need for New Indicators from Pharma and Beyond: Sant'Anna School of Advanced Studies, Pisa, Italy 15 - 16 May 2010. May 2010.

¹⁵ The Economist Intelligence Unit - The Future of Healthcare in Africa 2011.

capacity to help ease the problem of access in the long term. For example, UNAIDS published an Issue Brief in January 2012 in which it identified local production of HIV treatments as being critical for the long term sustainability of the HIV/AIDS response¹⁶.

1.1.7 Limited access to essential medicines

Compounding the disease burden and the shortage of human resources for health is the fact that many people still do not have access to the essential medicines they need. This is a result of a multitude of factors, including the lack of local production capacity, weak institutional capacity and poorly regulated supply chain systems that enable sub-standard products (locally produced and imports) to reach patients, and the emerging scourge of Africa's insidious public health crisis - counterfeit drugs. As a consequence, access to essential medicines in Africa has been hampered because products are not available, not affordable, or ineffective, amongst other reasons.

For example, the availability of medicines at the retail pharmacy level in most Organisation for Economic Co-operation and Development (OECD) countries is over 90%. In Africa, it is estimated that the availability of essential medicines (excluding North Africa) is way below 40% in the public sector, which caters for the bulk of the population, and less than 60% in private sector medicines outlets¹⁷. The end result is poor access to essential medicines with the resultant poor health outcomes. Notwithstanding the fact that there has been considerable progress – especially in the treatment of HIV/AIDS, TB and malaria - anecdotal evidence from across the continent suggests that the observation made in 2001 in a WHO/World Trade Organization (WTO) briefing paper, as captured below, still holds:

“In Africa and South East Asia, prompt diagnosis and treatment could save an estimated four million lives each year. Two-thirds of all deaths of children under 15 are due to seven diseases for which effective prevention and treatment exist. Put simply, people are dying because the drugs they need are not available to them. The opportunities for rapid health gain through better access to health technology are immense”¹⁸.

It is a matter of concern that, even when medicines are available, their quality is suspect due to the weak nature of regulation and widespread non compliance with international Good Manufacturing Practice (GMP) and other critical components of the quality system. There have been a limited number of surveys on the quality of drugs in Africa with most focusing on products for the high profile pandemic diseases such as tuberculosis and malaria^{19,20}. Despite the lack of information across the much broader range of drugs required for a functioning health system, there is already a critical mass of evidence to suggest that the impact of sub-standard drugs is grave. For example, a recent WHO study²¹ looking at product quality of anti-malarial products in selected African countries found that 39% of products tested in Ghana were sub-standard and the proportion was as high as 64% of products tested in Nigeria (the samples taken included imported as well as locally produced drugs).

¹⁶ AIDS Dependency Crisis, Sourcing African Solutions – UNAIDS publication. January 2012

¹⁷ Rockefeller Foundation, Dalberg and MIT Zaragoza; 2008. Private sector role in health supply chains. Report available online at http://www.dalberg.com/html/PDFs/Health_Supply_Chains.pdf (accessed October 2011)

¹⁸ WHO Secretariat. 2001. More Equitable Pricing for Essential Drugs. Background paper for the WHO-WTO Secretariat workshop on differential pricing and financing of essential drugs.

¹⁹ A summary of the major prevalence surveys for sub-standard drugs can be found in J. M. Caudron et al's paper – Substandard medicines in resource-poor settings: a problem that can no longer be ignored. Tropical Medicine and International Health Volume 13 No. 8, pp 1062-1072, August 2008.

²⁰ A non-exhaustive list of publications on poor quality medicines can be found on QUAMED's website: <http://www.quamed.org/en/news-articles/quamed-factsheet-on-access-and-quality.aspx>

²¹ Survey of the Quality of Selected Antimalarial Medicines circulating in Six Countries in Sub-Saharan Africa. WHO, January 2011

There are those who say Africa need not bother with local production as affordable quality medicines are readily available from the East. The inherent weakness with this view is, firstly, that the current WHO prequalification system is limited to a very narrow range of essential medicines (HIV/AIDS, TB, malaria, pandemic flu, opportunistic infections, zinc sulphate, and some oral contraceptives), whilst the oversight of all other products used on a daily basis depends largely on National Medicines Regulatory Authorities (NMRAs), many of whom face serious structural, functional and capacity constraints. Secondly, there is evidence that many of the leading Asian companies are shifting their focus to the more lucrative markets of the West and may leave a gap that would be filled by second and third tier companies who may not necessarily have the same quality credentials. Where regulatory oversight is less strong (i.e. for products that are not assessed by the WHO prequalification process or by stringent regulatory authorities), there is strong anecdotal evidence and some empirical evidence to attest to the fact that sub-standard imports are already significant in many markets.

An American Enterprise Institute (AEI) working paper²² reports the results of products tested for quality in Africa and identifies the source of products found defective by the author, as reflected in the following figure:

Figure 3: Table from AEI working paper by R. Bate

	Total samples tested	Total samples failing Raman spectrometry	Percent failed
Large Indian Producers ^a	471	6	1.3%
Small Indian Producers ^b	327	29	8.9%
Chinese Producers	169	13	7.7%
Southeast Asian Producers ^c	69	4	5.8%
Western Producers ^d	438	1	0.2%
African Producers	302	28	9.3%
Producers in Mid-income Nations ^e	62	7	11.3%
TOTAL	1838	88	4.8%

a. More than \$300 million in annual revenue
b. Less than \$300 million in annual revenue
c. Countries include Thailand and Vietnam
d. Countries include those within European Union, as well as Switzerland and United States
e. Countries include Brazil, Turkey and Russia

Source: AEI Health Policy Working Paper

Faced with these challenges, the PMPA presents an opportunity to develop the local pharmaceutical industry and to enable it to respond to the needs of our continent for affordable, high quality essential medicines. The projected disease figures highlighted above are indicative of future demand patterns and, when taken with other projections on the economic outlook for Africa, speak to the future viability and strategic imperative of our pharmaceutical sector. They also clearly underline the need for planning today for an industry that will be able to respond to the needs of Africa tomorrow. Most importantly, the figures point to the need for planning for healthcare systems that cannot overly rely on donations and the goodwill of donors whose focus may shift and whose ability to support programmes indefinitely is coming under question in the current economic climate.

²²Bate, R. Are Drugs made in Emerging Markets good quality? AEI Health Policy Working Paper. December 22 2010. <http://www.aei.org/paper/100178> (accessed January 2012).

1.2 THE PHARMACEUTICAL MANUFACTURING PLAN FOR AFRICA

In recognition of the enormous challenges facing healthcare systems, including lack of access to essential medicines, and the reliance on others for solutions, our Heads of State directed the African Union Commission to develop a pharmaceutical manufacturing plan for the continent. The PMPA was duly developed and adopted by the Conference of African Ministers of Health held in Johannesburg, South Africa in April 2007 and endorsed by the Heads of State and Government in Accra, Ghana in July 2007.

The PMPA is premised on the inalienable principle that access to quality healthcare, including access to all essential medicines that are affordable, safe, efficacious, and of good quality, is a fundamental human right. The PMPA proposes that the promotion of industrial development and the safeguarding and protection of public health are not mutually exclusive priorities and that the production of quality medicines and the development of an international GMP compliant industry in Africa are possible, desirable and eminently doable. This Business Plan is based on the belief that industrial development and the development of the pharmaceutical sector is not in conflict with public health imperatives and that the industry should in fact be developed with the long term aim of promoting access to quality essential medicines.

The core objective of the PMPA is to support local pharmaceutical manufacturing in order to contribute to the following outcomes:

- Increased access to affordable quality medicines
- Sustainable supply of essential medicines

and it should have the following impact:

- Improved public health outcomes
- Industrial and economic development

This vision, as articulated in the inception report adopted by the AUC PMPA Technical Committee in December 2011, is to develop a competitive and enduring integrated pharmaceutical manufacturing industry in Africa able to respond to the continent's need for a secure and reliable supply of quality, affordable, accessible, safe and efficacious medicines.

The vision calls for the planning of today to be informed by the Africa of the future; an Africa that is on a high-speed train to prosperity and that will be able to afford to pay for medicines needed by its peoples. It also recognizes the ongoing human tragedy on our continent regarding the limitations in access to medicines and seeks to help address this situation through the development of the pharmaceutical industry. It is a vision that demands courage, foresight and the willingness to take tough decisions now in order to deal with the myriad of challenges that the pharmaceutical manufacturing system currently faces. Such initiatives will enable the industry to make the contribution to improved public health on the continent of which it is capable and will contribute to Africa truly becoming self sufficient in the provision of healthcare. This is a plan that foresees the entry of Africa into new drug discovery and the development and commercialisation of African developed and researched blockbuster drugs. It also recognizes the critical need for governments to play a catalytic role in order to kick-start the growth of the industry and to put a brake on overreliance on imports.

This vision leads to a path that calls forth Africans in the Diaspora to come back home and invites people of goodwill and funders of research to invest in African research and development work. It requires that governments give the upstream support needed to grow the industry and to assist it to realize its full potential. The vision calls for a path that leads to success, sustainability and self-sufficiency in the provision of affordable quality medicines.

The key factors that will enable our pharmaceutical industry to be successful in delivering on this vision include:

- Strong independent and predictable regulatory systems
- Availability of the requisite human skills and access to know-how in the short term
- Increased competition leading to continuous product improvements, increased production and distribution efficiencies, enhanced sales and marketing efforts and service and business model innovation
- Reduced demand uncertainty and accurate forecasting
- Enhanced regulatory oversight
- Investment and access to affordable finance
- Provision of time-limited, easily understood, and accessible incentives

Finally, the success of the PMPA vision will depend on a recognition that, whilst this is the overarching continental sector strategy document and road map, there are multiple ongoing efforts on the ground and that some Regional Economic Communities and countries have already developed and are implementing strategies and plans for developing the industry in their regions. The package of solutions proposed here is not intended to supplant or take precedence over the work already being done but will be deployed, as requested, to augment and plug into regional and country specific initiatives. Where there are no sector strategies in place, the AUC and our partners, subject to invitation, will look to assist in developing and implementing them.

Similarly, it is recognized that there are a host of development partners, Non Governmental Organizations (NGOs), African centres of excellence and others already engaged in various activities including regulatory harmonization, skills development, technology transfer and so forth. The AUC believes that in implementing this Business Plan, the coordination and integration of these various initiatives will be critical.

1.3 BUSINESS PLAN

The 4th Conference of African Ministers of Health directed the AUC to develop a Business Plan for the ‘operationalization’ of the PMPA, a directive which was further emphasized by the 5th Conference held in Namibia in 2011. The African Union Commission convened a stakeholder workshop in N’Djamena, Chad, to review the Terms of Reference (ToR) which should guide the development of the Business Plan for ‘operationalizing’ the PMPA.

The Chad workshop reconfirmed that the overall objective of the PMPA is to support local pharmaceutical manufacturing in order to contribute to:

- A sustainable supply of affordable quality essential medicines
- Improved public health outcomes
- Industrial and economic development

Although there is recognition of the importance of this Business Plan to achieving the stated objectives of the PMPA, the AUC acknowledges that it is not a panacea that will solve all challenges and that its impact will ultimately also depend on other initiatives, including the strengthening of health systems, developing human resources for health, and upgrading the distribution infrastructure in order to be able to effectively deliver drugs to all points of care.

1.3.1 Partnerships

Given the need to coordinate and integrate work on the PMPA, the AUC invited UNIDO to partner it in developing this Business Plan and to assist in the planning, organisation and coordination of the Plan's implementation. However, the Commission is acutely aware that there is no single organisation with the breadth of expertise to deliver on the Business Plan on its own. The AUC will therefore need the support and collaboration of various partners in this endeavour. Initial discussions are ongoing with potential core partners including the World Health Organization (WHO), the United Nations Joint Programme on HIV/AIDS (UNAIDS), the U.S. Pharmacopeial Convention (USP), the African Network for Drugs and Diagnostics Innovation (ANDI) and some of its centres of excellence, Saint Luke Foundation / Kilimanjaro School of Pharmacy and various academic entities (in Africa and beyond).

One component of the overall PMPA is the work being conducted by the New Partnership for Africa's Development (NEPAD), the World Bank, WHO and the Bill and Melinda Gates Foundation on registration harmonization through the African Medicines Regulatory Harmonization (AMRH) initiative. This work is well advanced with, for example, the launch of the regional strategy for the East African Community (EAC) which took place in March 2012.

Defragmentation of our markets through harmonization of registration requirements and further progress toward regulatory harmonization is vital for the long term sustainability of local production. With this in mind, the broader requirements for strengthening local production on our continent, as outlined in this Business Plan, will be closely coordinated with the ongoing work under the AMRH initiative.

The AUC recognizes the critical importance of political commitment and leadership at the highest levels and the need for inclusivity and proper coordination as prerequisites for success. We will therefore seek to align and integrate the efforts of all key partners behind the PMPA vision and the Business Plan since history suggests that 'isolated' and/or vertical programmes do not have the sustainable and substantive impact that can be achieved through cooperation. The nature of the pharmaceutical industry is such that manufacturers' viability is dependent on, amongst others, a product portfolio that cuts across a range of therapeutic

categories. Moreover, the sustainability of affordable high quality local production is dependent on coordinated change across the whole pharmaceutical manufacturing system.

The PMPA is a vehicle through which the AUC will mobilize the requisite resources and behind which various partners will align to provide technical support and insights in order to assist those member states who aspire to high quality sustainable local production. For those countries that do not have the ambition or capacity for developing their pharmaceutical industry, the PMPA will work on other initiatives to help strengthen quality and market surveillance systems. This approach will improve access to medicines in those countries that could source high quality, quality assured products from manufacturing hubs in the region.

It is envisaged that, in order to realize the ultimate vision of the PMPA, concerted action will be required over an extended timeframe (15+ years). Nonetheless, significant progress is still possible over the next five years. This Business Plan is weighted towards the near to medium term, keeping the long term objectives as the target, and it represents an approach for the first five year phase starting in 2013.

1.3.2 Methodology and Structure

The purpose of this Business Plan is to present the proposed approach for the operationalization of the PMPA. It outlines a number of interventions or a 'package of solutions' to address the various challenges faced by stakeholders associated with the industry if they are to contribute to the development of a sustainable pharmaceutical sector capable of responding to our continent's need for affordable essential medicines of good quality.

The proposed package of solutions is based on the findings of extensive desk research and consultations with stakeholders in various member states and with international experts. It also reflects consultations with various institutions engaged in one way or another with the pharmaceutical industry. Fact finding missions were undertaken to various member states in all parts of the continent. These visits incorporated consultations with a broad array of stakeholders, including national medicine regulators; officials from ministries of trade, industry, and health; government officials responsible for pharmaceutical policy and planning and industrial strategy; procurement officials and government central medical stores or tender boards; investment promotion agencies; pharmaceutical trade associations; and individual manufacturers.

The solutions are also informed by UNIDO insights acquired through activities carried out, including advisory services on policy and sector strategy development in countries like Ghana and Kenya; institutional support to organisations like the Southern African Generic Medicines Association (SAGMA), the West African Pharmaceutical Manufacturers Association (WAPMA), assisting the Saint Luke Foundation / Kilimanjaro School of Pharmacy in Tanzania in the development of human resources; and support to companies in Ghana and Cameroon. It is further informed by the work of the World Health Organization, the African Network for Drugs and Diagnostics Innovation (ANDI), the various AUC Technical Committee reports and the AUC PMPA Chad workshop; by AMRH and knowledge acquired through the New Partnership for Africa's Development (NEPAD); the work of the USP; and ongoing work to explore the economics of production and to establish partnerships with organisations like the World Bank, USP, WHO, and various African and international universities.

The Business Plan incorporates knowledge gained from this research and it has identified challenges and problems that will be addressed by the PMPA. There are general themes that, to a greater or lesser extent, are relevant in specific contexts but there is also a large degree of heterogeneity of the pharmaceutical manufacturing systems across our continent and these are reflected in the flexible structure that is proposed.

The remaining parts of this document are structured as follows:

Chapter 2 focuses on the current state of African pharma and key challenges and opportunities for its development.

Chapter 3 discusses proposed interventions ('package of solutions') to be undertaken under the PMPA.

Chapter 4 outlines the implementation plan and estimated resource requirements.

1.4 SUMMARY OF CHAPTER 1

Key messages from Chapter 1 include:

- The status of the pharmaceutical sector varies dramatically across our continent
- In sub-Saharan Africa, we face a huge infectious disease burden and a growing prevalence of chronic and non-communicable diseases
- In the North, the disease profile is similar to that of the West, with cardiovascular disease, cancer and diabetes being key public health concerns
- Our continent is predicted to experience strong economic growth over the coming years which should enable us to address some of the current limitations of our healthcare systems and to improve access to essential medicines
- At present, many of our healthcare systems face major challenges including underfunding, overreliance on donors, shortage of human resources, limited access to essential medicines and significant penetration of sub-standard and counterfeit products
- As a means of addressing the access to medicines challenges in Africa, the Pharmaceutical Manufacturing Plan for Africa was adopted by the Conference of African Ministers of Health in April 2007 and was endorsed by the Heads of State and Government in Accra in July 2007
- The objectives of the PMPA are to increase access to affordable quality medicines and to ensure a sustainable supply which will provide improved public health outcomes as well as deliver associated economic development
- Following the directive from the Conference of African Ministers of Health held in Namibia in 2011, the AUC was tasked with developing a Business Plan to operationalize the PMPA

- A stakeholder workshop in N'Djamena in June 2011 established the Terms of Reference for the development of the Business Plan
- UNIDO was invited to assist the AUC in developing this Business Plan
- Partnerships with various institutions and ongoing initiatives are essential for the genuine progress of our pharmaceutical industry. This Business Plan recognizes the progress made by the AMRH initiative as well as other African initiatives and institutions such as ANDI, the Kenya Medical Research Institute (KEMRI) and the Saint Luke Foundation, as well as by international development partners such as UNIDO, WHO, UNAIDS, and USP
- The Business Plan has been developed based on established expertise from various actors and through a consultative process that involved discussions with a wide range of stakeholders (ministries, regulators, academia, private sector) in member states from all parts of our continent

2. OVERVIEW OF PHARMACEUTICAL MANUFACTURING IN AFRICA

2.1 INTRODUCTION: THE PHARMACEUTICAL MANUFACTURING SYSTEM

The context within which pharmaceutical manufacturing operates in a country is determined by a number of stakeholders. Figure 4 provides a schematic representation of the roles and influence of key actors. This figure identifies the functions of the regulator who should ideally provide oversight of the quality systems throughout the value chain of pharmaceutical production and distribution. It also provides indicative examples of the tools that various government ministries have at their disposal for influencing the context within which the industry operates and recognizes that trade associations have an important role to play. In addition, it demonstrates that the system is not self contained within a country as imports compete with nationally produced products and the nature of export markets is defined by a similarly complex interplay of different institutions that set policy, provide regulatory oversight and possibly offer support to local actors. The impact of the international donor funded markets is also taken into account. For products supplied to these markets, regulatory approval and oversight is largely a function of international actors (although registration at the national level should be required as well) and procurement policies are defined by funding entities such as the Global Fund and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR).

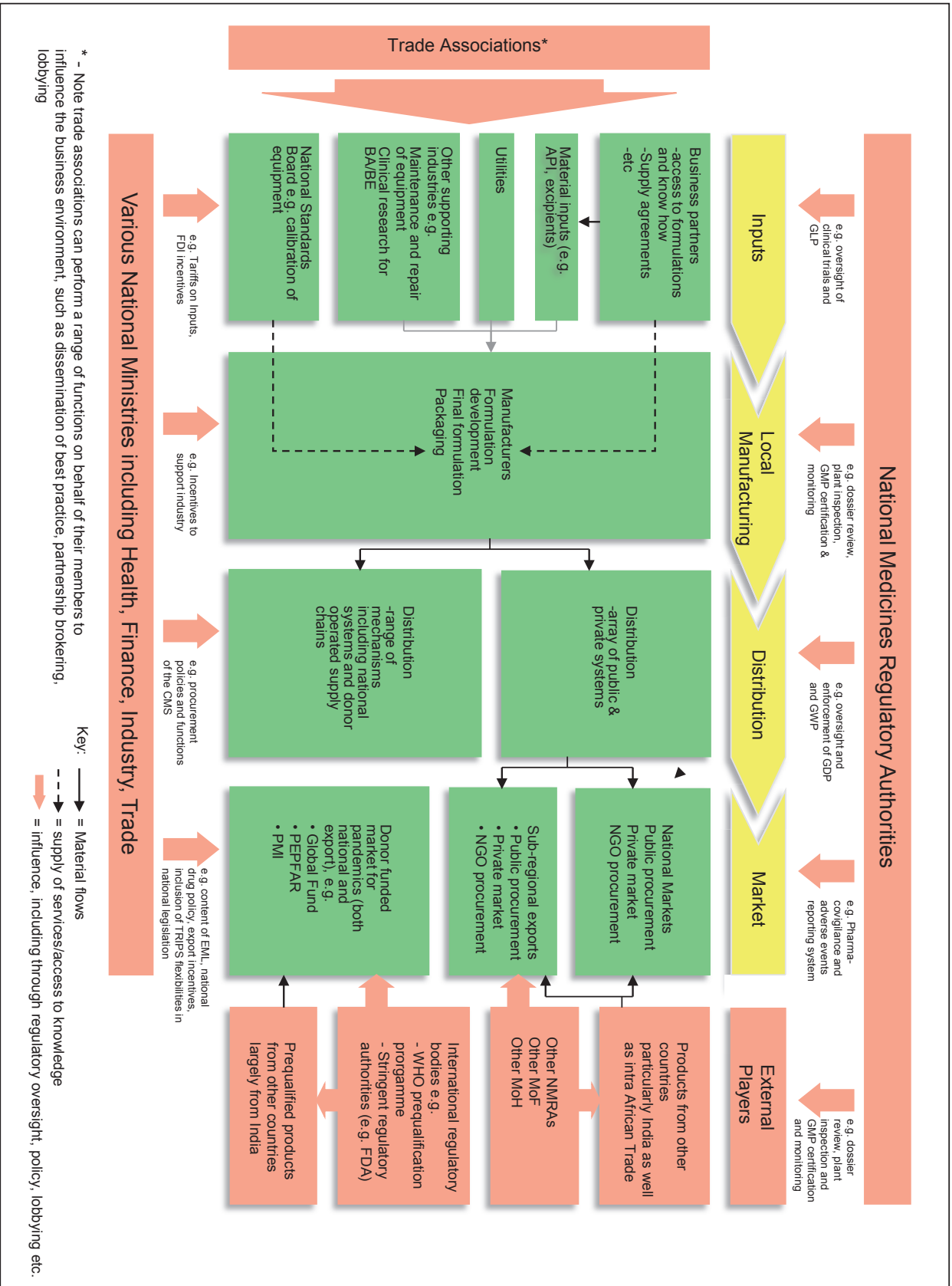
It should be noted that Figure 4 deals only with the system relating directly to the in situ value chain of generic drug manufacturing. For example, in order not to overcomplicate the picture, other stakeholders who play a less direct (although often extremely important) role have been omitted. Specifically, the manufacturing processes, regulatory functions, and policy making in this field all involve specialized skills. Therefore human capital and the institutions that develop and provide that human capital for the system are of great importance.

Pharmaceutical manufacturing is also a capital intensive activity and access to capital is another key aspect that, for simplicity, has been omitted. There are a variety of sources and mechanisms by which companies can access capital and, to some extent, the appetite of those different sources (e.g. equity investors, providers of debt, foreign direct investment, etc.) for engaging with the pharmaceutical industry is dependent on the dynamics of the rest of the pharmaceutical manufacturing system in a country.

The actual manufacturing systems in place in different countries vary from this schematic, which shows a somewhat idealized representation given that, for example, most NMRAs do not have the capacity to fulfil the range of functions that should be in place. Similarly, trade associations may not exist, and policies from different government entities may not be aligned behind a strategy in support of the sector. The current status of the key dimensions of the pharmaceutical manufacturing system across our continent is described in the following section.

It is the interplay of the different components of the manufacturing system that determines aspects of pharmaceutical production, including competitiveness and quality of production. These particular aspects are key if the fundamental objective of the PMPA of improving access to high quality drugs, whose production is sustainable (i.e. competitive with alternative sources of supply) is to be achieved. They are also critical for countries that aspire to export to developed markets. Further, a functioning manufacturing system has the potential to produce a broader range of drugs than is currently produced by most of our countries engaged in local manufacturing.

Figure 4: Schematic Representation of the small molecule 'Pharmaceutical manufacturing system'



2.1.1 The manufacturing system and quality

The 'quality' of pharmaceuticals is a function of many dimensions including, for example:

- The level of active pharmaceutical ingredient (API) content
- Appropriate formulation impacting on the pharmaco-kinetics of the drug (e.g. peak concentration, dissolution profile of drug)
- Degradation of the product due to many possible factors such as poor production or inappropriate storage and distribution
- Contamination of the product with other drugs, with impurities, or following the degradation of the API, for example, during transport or once it has been formulated
- Mislabelling of products
- Microbial contamination of product

This is only an indicative list of some of the areas where product quality can be compromised. In the developed world, the risk of such failures occurring and of sub-standard products actually reaching patients is minimized by a complex interplay of regulatory oversight that enforces concepts such as Good Manufacturing Practice (GMP) and other aspects of the quality system including Good Laboratory Practice (GLP), Good Distribution Practice (GDP), etc., as well as conducting pharmaco-vigilance activities to monitor products on the market.

Another vital element is having a functioning and efficient adverse event reporting mechanism such that problems can be rapidly identified and resolved. A fundamental philosophy required for the pharmaceutical supply chain is that quality is manufactured into the product at all stages and that inspection and quality control at the end of the production process is not sufficient; it is just one part of an integrated approach to quality assurance.

The safety and efficacy of a product are not only a function of the processes followed in its production and distribution and their regulatory oversight. These processes are intended to ensure that products are manufactured consistently according to the specifications described in the product dossier reviewed and approved by the regulator prior to marketing authorization being granted. Consequently, review of detailed evidence to confirm the manner in which the product behaves when given to patients is another important component of ensuring that products are safe and effective.

Most products on the Essential Medicines List (EML) are no longer covered by patent protection and generic versions can be legally produced without the need for voluntary licences from originator companies. A generic product is given marketing authorization on the basis that it is therapeutically equivalent to the originator product. This means that large scale clinical trials of generics are not required but that evidence to attest to their equivalence to the originator product is. In most cases, the necessary evidence is a bioequivalence study in which clinical trials are conducted to show that the generic product behaves in the same way as the originator when given to patients. In some cases where, for example, an active ingredient is highly soluble, approval can be granted on the basis of a biowaiver, where non-clinical evidence of the physical and chemical properties of the product are shown to be equivalent to the originator. Samples of products also need to be tested at quality control laboratories prior to marketing approval being granted.

Therefore, the components of the manufacturing system required to ensure quality of production and safety of the product are adherence to GMP by the manufacturer (which includes design of the plant, maintenance and integrity of equipment, established and validated processes and procedures for all aspects of production and quality control at various stages of the production cycle); development of the formulation that is to be manufactured with accompanying evidence to attest to the equivalence of the product to the originator; detailed review of the dossier and sample testing by the regulator prior to marketing approval; and regular inspection of production processes by the NMRA at the manufacturing site. Following production, the regulator also plays a key role in ensuring that the product reaches the patient in an appropriate condition through oversight of Good Distribution and Wholesaling Practices. A further post production function of the regulator is overseeing the market through pharmaco-vigilance activities and the establishment of adverse event reporting mechanisms. This is required to identify instances of sub-standard products reaching the market so that product recalls can be rapidly enacted and counterfeit products identified and removed from the market.

2.1.2 The manufacturing system and competitiveness

The increased investment and operating costs involved in setting up and running a GMP compliant facility do not mean that international standard production on our continent cannot be competitive or that very large manufacturing plants are required to achieve cost effective production. Research commissioned by UNIDO indicates that the economics of pharmaceutical production are highly complex. This as yet unpublished working paper indicates that fixed costs associated with upgrades are generally directly correlated to the output of the facility such that technical economies of scale are not particularly significant beyond certain fairly low volumes. In fact, established wisdom that a capacity of 1.5 billion tablets is necessary for competitive production is not borne out by the analysis.

Further, the significance of fixed costs means that capacity utilization has a critical impact on the cost of each unit of production. The nature of pharmaceutical production is that it is a batch process where different products are manufactured with the same machinery. Changeover time required between batches of different products represents downtime when assets are not being productively utilized. Machine downtime can also occur where a production line is not balanced. For example, one piece of equipment may have a greater output per unit of time than another leading to a bottleneck situation where the machine with the greater output remains idle for periods of time. Downtime can also occur due to breakdown of equipment but preventative maintenance programmes can minimize the impact of this.

Modern business practices have evolved methods by which downtime of equipment can be kept to a minimum and capacity utilization optimized. This can, for example, involve campaigning batches of the same product so that limited changeover time is required. The degree to which campaigning can take place to achieve efficiency of production is to some extent also a function of the market (size and procurement agreements) as another important component of the economics of production is working capital requirements, in which inventory carrying costs (inputs, work in process, and retained final products) are critical.

The above comments refer to the manufacturing of approved products. However, the cost of developing new products is significant, particularly if bioequivalence studies are required. Companies can buy dossiers on the open market and go through a technology transfer process to set up production in their facility. However, the cost of high quality dossiers can run to US\$100,000 and more.

These issues and the mechanisms by which the PMPA Business Plan can take them into account and instigate solutions that enable competitive high quality production are explored further in the ‘challenges’ part of this chapter and in the ‘solutions’ chapter (Chapter Three).

2.1.3 The manufacturing system and breadth of product portfolio

The pharmaceutical manufacturing system described above can produce most off patent pharmaceutical products (excluding, for example, biological products and blood products). Moreover, by using TRIPS flexibilities or voluntary licences, even critical health products still under patent protection, like second and third line antiretroviral drugs (ARVs), can be manufactured. Products that involve novel combinations of active ingredients or new formulations (e.g. paediatric formulations) can also be produced through this system.

From a public health perspective, key products that a country’s health system needs to source are listed in the WHO Model List of Essential Medicines, which countries can adapt to their specific circumstances. The EML lists over 300 products across many disease indications including analgesics, anti-allergy medicines, antibiotics, anti-helminthics, anti-TB drugs, anti-fungal drugs, ARVs, malaria treatments, various products for tropical diseases such as those to treat African trypanosomiasis, anti cancer agents, treatments for cardiovascular disease, gastrointestinal medicines, treatments for psychiatric disorders, drugs for respiratory disorders, products for the treatment of diabetes and others. The WHO also has a Model List of Essential Medicines for Children, which includes over 250 products across a similarly broad range of indications.

These products cover different formulation types including tablets, capsules, syrups, ointments, gels, small and large volume parenterals, and dispersibles. The underlying quality principles and the economics of production remain similar across formulations (although for parenterals, for example, the need for sterility requires enhanced GMP). However, the equipment required for various product types varies and the market dynamics for different medications (e.g. volume requirements, level of competition, etc.) also vary. Over and above the EML, there are many other products that are off patent and which Africa-based manufacturers could produce for local consumption and ultimately for export to other developing and developed markets. Some companies in countries such as South Africa and Tunisia have, for example, been certified by American and European regulators.

2.2 THE CURRENT STATUS OF THE PHARMACEUTICAL INDUSTRY AND OTHER STAKEHOLDERS

This section describes the size and current levels of activity in the different segments of the pharmaceutical industry. It also details the status of the various components of the manufacturing system as they stand today, before outlining the challenges faced by different industry players.

2.2.1 Industry size and participants

The African pharmaceutical market accounts for only a small portion of the global pharmaceutical industry. In 2007, the International Finance Corporation (IFC) estimated that sub-Saharan Africa accounted for just under 0.6% of the global market or US\$3.8bn²³, whilst the North African market is valued at several more billions. Recent estimates for the whole continent put the market at between US\$8bn to US\$10bn. IMS Health recently estimated that the Nigerian market was worth US\$2.5bn in 2011 and that the African market as a whole will be worth about US\$24bn by 2014²⁴. The pharmaceutical market in the Republic of South Africa is now worth over US\$4bn²⁵. Estimates of the value of the pharmaceutical market on our continent vary significantly as a result of different methodologies and this is also indicative of the paucity of data.

Although, by any measure, the African pharmaceutical market is small compared with the global market, it plays host to some of the leading global innovator and generic manufacturers and has a growing number of local manufacturers. The majority of African manufacturers are small privately owned companies that mostly serve their national markets. However, there are also examples of publicly listed companies (e.g. Ayrton and Starwin in Ghana) and some companies that have invested in their facilities through accessing international equity financing (e.g. Universal in Kenya). There are also domestic manufacturers that are comparable in size to leading international generic manufacturers. For example, Aspen in South Africa is in the top ten largest generic manufacturers in the world. Furthermore, manufacturing of pharmaceuticals on our continent is not exclusively the purview of the private sector. We have public sector manufacturers such as Sidal (80% state owned) in Algeria and Saphad in Tunisia, which is also majority government owned. Mozambique has a government owned liquid facility and is currently in the process of constructing an ARV plant with the help of Brazil.

A further example of direct government involvement in pharmaceutical manufacturing is a recent development which saw a US\$211mn joint venture (Ketlaphela) being formed between Lonza, a leading global API manufacturer from Switzerland, and the South African government (through Pelchem) for the production of ARV APIs in South Africa. In the field of vaccine production, the South African Government has also formed a Public Private Partnership called The Biovac Institute.

Currently, there are an estimated 38 countries that have pharmaceutical manufacturing entities on the continent. The size of the sectors in these countries is widely divergent. For example, Nigeria has more than 200 registered pharmaceutical manufacturers, South Africa has roughly 30 domestic producers, and Ghana and Kenya have an estimated 20 and 40 active registered manufacturers respectively. Algeria has roughly 30 manufacturers and Tunisia about 20. Other countries such as Uganda, Tanzania, Zambia and Zimbabwe have dynamic but relatively small sectors with between five to ten active companies. There are also countries such as Cameroon, Namibia, Swaziland, Lesotho, Malawi and others that have just one or two active manufacturers.

In addition to local manufacturers, there are many importers and distributors of medicines who import from and represent companies from across the world, with India and China being the predominant suppliers. Further, the leading global innovator (Pfizer, Sanofi, GSK, Merck) and generic (Ranbaxy, Aspen, Mylan, Cipla) companies either have a direct

²³ IFC – The Business of Healthcare in Africa 2007

²⁴ IMS Health Market Prognosis 2010

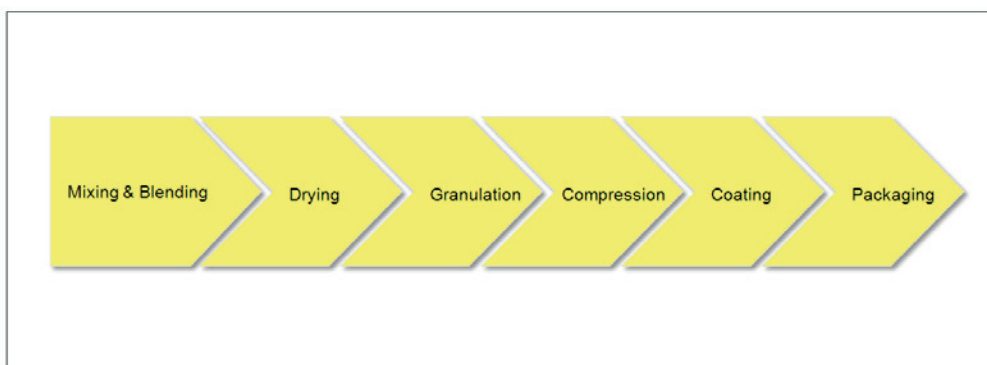
²⁵ IMS Health TPM 2011 and South African National Treasury Contract Management figures

presence or work through agencies and distributors. Some of these leading pharmaceutical companies have manufacturing facilities in various African countries. They include, among others, GSK, Johnson and Johnson, Sanofi (with plants in six African countries), Sandoz and Ranbaxy. The latter now has three manufacturing facilities situated in South Africa, Nigeria and Morocco.

A few international companies are also involved in joint ventures with local manufacturers and some of these have involved the transfer of technology and the licensing of products to African players. They include leading global generic companies like Cipla, which has an arrangement with Quality Chemicals of Uganda, Zydus Cadila, which is in collaboration with Almeta Impex of Ethiopia, and Ranbaxy, which is working with Community Investment Holdings of RSA. This trend is not confined to local companies only. Whilst not a fully-fledged joint venture, Sanofi Aventis in South Africa recently announced an agreement wherein Hetero of India will supply it with raw materials for the manufacture of ARVs for local consumption²⁶. Sanofi Pasteur (the vaccine arm of Sanofi Aventis) has recently announced a technology transfer agreement with the The Biovac Institute in South Africa.

Figure 5 is a schematic that represents the typical activities of local manufacturers and demonstrates that the industry is largely involved in formulating imported raw materials. In fact, some companies even procure ready-made granules and simply start at the compression stage. This is just one example and other types of formulations are produced including capsules, liquids, large and small volume parenterals and ointments. The exceptions to the focus on final formulation and packaging are South Africa²⁷ and Egypt²⁸, which have commercial scale production of a limited range of APIs²⁹. There is also small scale API manufacturing for internal consumption in Ghana for the production of azithromycin API³⁰.

Figure 5: Typical operations of a local oral solid dosage form manufacturer



2.2.2 Range of products manufactured in Africa

As with other areas covered by this Business Plan, the range of products varies significantly across our countries. The Republic of South Africa and North African countries have well developed industries with participants producing a broad range of products. The majority of

²⁶ <http://www.businessday.co.za/articles/Content.aspx?id=168895>

²⁷ Fine Chemical Corporation – www.fcc.co.za

²⁸ The Pharma Letter - Egypt's pharma market set for 11.4 per cent CAGR to 2014 - <http://www.thepharmalatter.com/file/95304/egypts-pharma-market-set-for-114-cagr-to-2014-helped-by-drug-pricing-reform-that-will-boost-generics.html> (accessed October 2011).

²⁹ Personal conversations with Dr. Alexandra Graham and Paul Lartey of Lagray Chemical Company

³⁰ A lifeline to treatment: the role of Indian generic manufacturers in supplying antiretroviral medicines to developing countries; Brenda Waning, Ellen Diedrichsen and Suerie Moon. Journal of the International AIDS Society 2010, 13:35

manufacturers in the rest of SSA produce a limited range generally covering nutraceuticals, cough and cold preparations, simple analgesics and sedatives, anti-malarials, older generation antibiotics, anti-helminthics and first generation anti-hypertensives, anti-diabetics and neuro-psychiatric drugs.

This mismatch between the EML and actual product portfolios supplied by local manufacturers represents a significant latent potential market for locally manufactured products in many parts of the continent. So long as quality standards are enhanced to meet international GMP (see solutions Chapter for a pragmatic approach), this would also represent an important opportunity for improved public health given the regulatory limitations and supply chain challenges that form the basic philosophy for why local production has such an important role to play. Expanding the range of high quality locally made products is an important dimension towards realizing this objective.

Arguably the most significant public health issue on a large part of our continent is HIV/AIDS. The majority of the market for ARVs is controlled by the international donor entities and Non Governmental Organisations (NGOs). Without exception, they require that products be prequalified by WHO or approved by a stringent regulatory authority. To date, few of our companies have supplied the international donor markets and it is estimated that 80% of ARV finished formulations on our continent are imported, with the majority coming from India³¹.

There are pockets of ARV production that serve markets other than those of international donors. For example, Danadams of Ghana won a tender from the West African Health Organisation (WAHO) to supply ARVs to The Gambia, Togo, Côte d'Ivoire and Burkina Faso. Danadams has also received emergency orders to fill requirements for donor funded programmes when supply chain and procurement failures have led to risks of stock outs of key products. Furthermore, there are a number of manufacturers in South Africa that supply ARVs to the national government-funded market. There are also other African manufacturers, who (despite operating to international GMP standards) have not yet applied for WHO prequalification as the international donor funded markets are viewed as unattractive. One reason given for this is the advantages from which Indian manufacturers in particular benefit in terms of government support. One company that has achieved international certification for an ARV commented that it could compete on price with Indian companies if there was a level playing field and the opportunity to campaign production batches.

Malaria is another critical public health concern. The range of products for treating the disease includes artemisinin-based combination therapy (ACT), such as artemether/lumefantrine (AL) and artesunate/amodiaquine (AA) now identified by WHO for first line treatment, as well as older generation products such as sulfadoxine/pyrimethamine (recommended for intermittent preventative treatment during pregnancy). There is a significant donor funded market for these products (with prequalification/stringent regulatory approval requirements) but also substantial private and government funded markets. Only one company in Africa is certified by WHO for an anti-malarial and therefore able to access the donor funded markets although many others have been supplying older generation products and, latterly, the ACTs to the other market segments.

Unlike most other product types, there have been a number of in-depth studies into the quality of drugs for the treatment of malaria. The output of such studies is very detailed and

³¹ A lifeline to treatment: the role of Indian generic manufacturers in supplying antiretroviral medicines to developing countries; Brenda Waning, Ellen Diedrichsen and Suerie Moon. Journal of the International AIDS Society 2010, 13:35

some of the specific results are recognized as lacking statistical significance. In view of this, sweeping generalizations need to be avoided. However, in the non-donor funded markets, evidence suggests that the quality of products is a serious concern (although there is substantial variance among countries). The evidence also suggests that significant proportions of imported products are sub-standard as well as some locally produced drugs.

The quality standards of our manufacturers vary dramatically and it would be unfortunate to conclude that all sources of domestic production of anti-malarials pose a public health threat. We need to make sure that all companies reach the standards of the leading players to ensure a reliable, sustainable source of effective anti-malarials. We cannot rely on imports from a diverse range of geographies since a significant proportion of such products have been found to be sub-standard (although, again, significant variance is seen among companies in terms of their failure rate).

Many commentators have identified the recent Affordable Medicines Facility for malaria (AMFm) as damaging to the long term sustainability of supply of quality medicines to fight malaria. In the short term, the Facility has led to more prequalified products being available in the countries in which it has been active. However, this has, in turn, severely reduced the anti-malarials market for our manufacturers, including for those who are demonstrably superior to some of the companies from which we have imported. The danger is that, when the AMFm ceases to subsidize these products, our local capacity will no longer be in place and we will have to rely on imports that cannot be properly regulated and have been seen in some instances to pose a risk to public health.

The international malaria community recognized the unintended consequences of this initiative and, in May 2011, the African Leaders Malaria Alliance (ALMA) convened a conference in Nairobi, Kenya to discuss the implications and appropriate action to minimize the long term potential downsides. Support for local industry to reach international standards and remain competitive across its product portfolios was a key recommendation of the meeting, a message that is consistent with the proposed approach of this Business Plan.

2.2.3 Access to inputs

African manufacturers depend on imports for the bulk of their production inputs. Furthermore, practically all the machinery and equipment, laboratory equipment and reagents, and production raw materials including API, aluminium foil for blister packaging, other labelling materials, and excipients are imported. The local contribution to inputs is confined in some countries to starches and sugars and it is estimated that almost 95% of the continent's API needs are met by imports.

This reliance on imports has very real and significant financial implications. The lead time required for goods to arrive from Asia means that credit terms offered by suppliers may be used up prior to the inputs even reaching manufacturers' warehouses let alone being converted into finished products and distributed to the market. The implications for working capital can be dramatic and, given the high cost of trade financing in many of our countries, ways of addressing this cash flow and cost issue will be one area where government intervention (for a defined period of time) could make a meaningful contribution to the viability of companies as the economic structure of the industry evolves into one that is sustainable in the long term.

2.2.4 Quality of production

There have been no published systematic studies on the range of quality standards to which manufacturers on our continent adhere. We know that production in RSA and North Africa is generally close to international standards with a significant proportion of players actually reaching international standards. Companies such as Medis in Tunisia are exporting products to the highly regulated European market and a company like Aspen Pharmacare exports to North America, Europe, South America and Australia among others. However, in other countries in SSA, the range of quality standards is more varied. There are two companies in the rest of SSA that have achieved WHO prequalification of a product (Varichem in Zimbabwe and Universal in Kenya) and Quality Chemicals in Uganda has been approved by WHO as an additional manufacturing site for some products that have been prequalified by Cipla in India.

There are also a number of companies that are striving to achieve international manufacturing standards with LaGray in Ghana, for example, having effectively achieved this as evidenced by the approach to the company of the United Nations Children's Fund (UNICEF) and PEPFAR for possible supply of products such as zinc sulphate and a lamivudine/zidovudine fixed dose combination ARV. Cosmos in Kenya has received certification from the Pharmaceutical Inspection Co-operation Scheme (PIC/S). In Nigeria, the National Agency for Food and Drug Control (NAFDAC) has been working with WHO and eleven companies, including May and Baker and Juhel Nigeria, to achieve international GMP standards and to have products prequalified by WHO.

There are other examples of companies in SSA striving to achieve international standards, with Cinpharm in Cameroon being an example of a company that is investing in upgrading. Further, there are a number of companies that are investing in new plants which are being purpose built with international GMP requirements in mind. These include Tanzanian Pharmaceutical Industries (TPI) which has constructed a state of the art facility in Arusha, Tanzania, and Azee Aqua and Lab and Allied, both in Kenya, which are constructing a large and small volume parenterals facility and an oral solid dosage forms facility respectively. Danadams is also in the process of constructing a new facility that is internationally GMP compliant.

There is evidence then that production to international standards is possible across our continent and that we have entrepreneurs with the appetite for risk, energy, and commitment to achieve these goals. However, as well as these (and other) leading players, we know that there are many other companies licensed to manufacture products whose quality systems fall in some cases way below what should be acceptable. Whilst there has been no systematic study, experts who have visited plants, and comments by regulators with access to confidential GMP inspection reports, provide categorical evidence that this is the case.

There are genuine challenges confronting companies that aspire to improve quality and to realize their ambition of achieving international GMP status. However, there are other manufacturers who are happy to maintain the status quo and produce to their current standards. Discussions with various regulators revealed that, in certain cases where they were aware of significant non-compliance, they were either reluctant to act or were prevented from doing so due to political interference.

It is encouraging that some NMRA's are working with industry to resolve such issues in a pragmatic manner and to effect corrections gradually in order to reach acceptable international standards. One such example is the work of NAFDAC in Nigeria and the Medicines

Control Authority of Zimbabwe (MCAZ). However, the operating environment of companies is affected by many interrelated aspects of the pharmaceutical manufacturing system of a country, many of which fall outside the mandate of the regulatory authority. This Business Plan proposes a systemic approach to developing the sector and identifies solutions to the various interrelated issues which, if implemented in a coordinated fashion, could support and perhaps accelerate these initiatives. Such solutions could also enable regulators in other countries, which aspire to become centres of excellence for pharmaceutical manufacturing, to take similar steps.

2.2.5 Efficiency of production

As already pointed out, the economics of pharmaceutical manufacturing are more complex than is perhaps generally realized. Key to the competitiveness of the industry is the efficiency of production. Various principles on achieving efficiency have been developed in countries like Japan and the US over the last few decades (across industry sectors) and they include approaches such as lean manufacturing, Total Productive Maintenance (TPM), 6 Sigma and the Toyota Production System (TPS). UNIDO has conducted pilot work with the aim of understanding how such approaches could impact on the competitiveness of the pharmaceutical sector in Africa.

Unpublished initial reports have been shared and, although the findings are based on a very limited sample and top-level analysis of leading companies (from a quality perspective), the output provides evidence that substantial efficiency gains could be achieved if Japanese-style production approaches were to be introduced. Rough estimates based on this analysis indicate that productivity levels could be improved by around 30%. However, the potential improvement will depend on the starting point of the company. One organization interviewed in the course of research for this Business Plan claimed to have been able to improve output fivefold through optimizing its production scheduling process, instituting a change management process, and training all employees on the imperatives for quality and efficiency of production.

There is then substantial scope to improve the competitiveness of production through implementing approaches such as TPM. However, actually realizing the benefits of such approaches requires expertise, 'buy in' across the organization from senior management to production staff, and the embedding of a culture of efficient production.

2.2.6 Status of regulatory oversight

Oversight of the market is a function of Medicines and Allied Substances Control regulations. These pertain to the regulation and control of various aspects of the pharmaceutical value chain, from medicine registration to how the end users access medicines. The regulations also speak to the functional and operational structures of the NMRA and define responsibilities, reporting structures, funding and so forth.

The functions of a regulator are many and include the following minimum functions³²:

- Making sure that the manufacture, import and export, distribution and wholesaling of all medicines are properly licensed and that there is conformance with Good Manufacturing Practice (GMP) and that Good Distribution Practice (GDP) is observed in all activities and on all premises

³² WHO Policy Perspectives on Medicines. No 7, 2003.

- Assessing the safety, efficacy and quality of all medicines prior to granting a marketing authorisation
- Conducting ongoing monitoring and surveillance of the quality and safety of marketed medicines to guard against harmful, sub-standard and counterfeit medicines being used by members of the public
- Inspecting and controlling the informal market, including internet-based trade, in order to prevent illegal trade in medicines
- The monitoring of the advertising and promotion of medicines and the dissemination of independent information on the rational use of medicine to public sector and health professionals
- Participation in forums in order to promote collaboration and facilitate the sharing of information and discussion of issues of common interest with other regulators at regional and international levels
- The continual monitoring and evaluation of performance to identify weaknesses, review whether objectives have been realized and to take corrective action where needed

Most African countries are not yet in a position to meet these basic minimum requirements. The key findings of a 2010 WHO Assessment of Medicines Regulatory Systems in 26 sub-Saharan countries³³ are summarized in Table 1 below.

The study concluded that there was adequate legal provision for:

- NMRAs' functions
- Medicines registration, relevant documents for applicants and assessors, advisory committees, and use of external assessors/expertise
- Licensing (manufacture, wholesale, distribution, etc.)
- Monitoring of safety, efficacy and quality of marketed medicines

but identified the following weaknesses:

- Complex legal frameworks, unclear definitions of responsibilities, and regulatory gaps and overlaps; some NMRAs are not fully established and in some countries they are not performing all regulatory functions
- Lack of funding, shortage of staff, lack of operational resources, no quality management systems, no staff development programmes
- Guidelines and assessment procedures not up to WHO standards
- Poor coordination among the various authorities/bodies involved in regulating the industry

³³ WHO. Assessment of medicines regulatory systems in sub-Saharan African countries. An overview of findings from 26 assessment reports 2010.

Nonetheless, there are countries on our continent that have more robust and fully functioning regulatory systems (although none is regarded as being stringent by international donors). For example, the Medicines Control Council (MCC) in South Africa is a member of PIC/S. Algeria has a rigorous inspection process whereby all batches manufactured in the country are tested by the Laboratoire National de Contrôle des Produits Pharmaceutiques (LNCPP), the national quality control laboratory which employs over 400 people.

Yet most African NMRA's face immense challenges, inter alia a severe shortage of funding and human resources, a high staff turnover and the consequent lack of experience in many core functions. They also suffer from antiquated filing and other administrative systems. The capacity issues in most regulatory authorities go beyond a shortage of inspectors and include lack of laboratories for monitoring (or ill-equipped laboratories) as well as the skilled personnel to operate them.

Table 1: Summary of findings from WHO report on 26 National Medicines Regulatory Authorities in Africa

Regulatory Framework	Structure & Management	Medicines Registration	Licensing of Activities	Import and export control	Inspection	Quality Control	Market surveillance	Oversight of Clinical Trials
Strengths								
Legal provisions for NIMRA and its functions (all)	An increased awareness of importance of independence, fairness, transparency Highly motivated & professional staff despite working conditions (all)	Legal provision for medicines registration, relevant documents for applicants and assessors in place, advisory committees in place, and use of external assessors/expertise	Legal provisions for licensing in place (manufacture, wholesale, distribution, etc.)	Only registered medicines were eligible for import	Structures in existence	Regulatory QC labs in place, with qualified staff and adequate equipment	Legal provisions in place to monitor safety, efficacy and quality of marketed medicines	Provisions for clinical trial control in place
Weaknesses								
Complex legal framework, unclear definitions of responsibilities, regulatory gaps and overlaps. Some NIMRAs not fully established and in some countries NIMRAs not performing all regulatory functions	Lack of funding, shortage of staff, lack of operational resources, no quality management systems, no staff development programmes No measures to ensure confidentiality and avoid conflicts of interest	Guidelines and assessment procedures do not meet WHO standards Wide ranging exemption clauses not justified by risk assessment e.g. donations of medicines Few mechanisms to ensure impartiality and technical competence of assessors No reliance on or recognition of decisions of SRAs despite resource challenges	Licensing not implemented efficiently and administered by entities other than the NIMRAs, some of which lacked any technical capacity There was poor coordination and information management which resulted in regulatory gaps	Absence of efficient systems to verify registration Poor coordination among authorities involved No mechanisms to control exported medicines	Inspections not well coordinated Guidelines not in line with WHO, GMP or GDP Lack of qualified inspectors as well as logistical difficulties limiting number and quality of inspections	Few had a QMS in place and QC testing not used optimally to complement other regulatory functions	Implementation poor and not prioritized based on risk. Few countries monitored adverse events This function was not well integrated with other regulatory functions	Few NIMRAs authorised the performance of clinical trials in their countries, little monitoring of clinical trials after approval, and weak or non-existent links with ethics committees GMP not assured for investigative products

In addition, the vast challenge of overseeing many thousands of products from numerous plants spread across different geographies (e.g. products from over 1,000 production sites registered in Kenya where the Pharmacy and Poisons Board has just six full time GMP inspectors) is impossible to meet the desirable level given the resource constraints. Similarly, the monitoring of the market through pharmaco-vigilance and post market surveillance is far from robust in most countries. This provides opportunities for counterfeit and sub-standard products, leads to adverse events often going unreported or undetected, and results in failures to recall defective products. International development partners such as USP and WHO have been helping to improve post marketing surveillance and, as part of this Business Plan, these initiatives will be built upon and augmented to rapidly enhance the oversight of the market place.

The entities charged with regulation of the pharmaceutical industry have a critical role to play in the pharmaceutical manufacturing system. International stringent regulators have substantial resources and a wealth of experience to mobilize in conducting the full range of regulatory functions. However, even the US' FDA faces capacity limitations as evidenced by the ever increasing time taken to approve Abbreviated New Drug Applications (ANDAs). Given the inherent capacity challenges faced by all regulators, and the particular resource constraints in many of our countries, we need to work together to maximise synergies (under the AMRH work) and to invest in the regulatory functions critical for public health protection and a market place that is fair and competitive. The proximity of high quality local production, coupled with targeted investment in our NMRA's, is a means by which we can maximise the ability of regulators to protect our people, especially when we are less and less reliant on donations.

2.2.7 Policy and legislative landscape

There are many policy and legislative tools that impact on pharmaceutical manufacturing and they are implemented by different ministries within government. One key instrument specific to pharma is a national drug policy, which is in place in most of our countries and normally has two core objectives:

- to promote access to safe, effective quality medicines at affordable prices
- to promote the rational use of medicines and EMLs

A further objective is often that of developing local industry via the promotion of local production of essential medicines. However, Ministries of Health (MoH) in isolation do not control the full range of instruments that impact on the ability of the local pharma industry to develop. Consequently, whilst promoting local production may be an ambition, without coordinated action across different ministries, there can be policy incoherence. Moreover, the objectives of the MoH may not be reflected in the activities of, for example, national revenue authorities or ministries of trade and industry.

Historically, where different priorities guide the work of different government ministries and departments, this has resulted in conflicting approaches to the pharmaceutical industry. Not many countries on our continent have an explicit strategy for the pharmaceutical sector which coordinates the tools at the disposal of different government ministries. As a result, there are frequent examples of conflicts in policy as implemented by different government actors. There are many different policy and incentive tools that governments can employ for various objectives yet, without specific consideration of how these tools affect the pharma

sector, policy incoherence is somewhat inevitable.

Countries with thriving pharmaceutical industries like India and China provide significant government support to their producers in the form of incentives and protectionist policies. Policy instruments that have been used to protect pharmaceutical sectors in developing regions include:

- High tariffs on imported finished products. For example, India is reported to have duties for final formulations of up to 56%; Brazil has a 15% tariff for finished formulations; and China has recently imposed import tariffs of up to 37% on Sulfamethoxazole (SMZ) imported from India³⁴
- Procurement preferences. Brazil has a 25% price preference and Russia has introduced measures to ensure that 70% of products procured by the state are locally manufactured. This has apparently led to many Indian companies considering putting up manufacturing plants in Russia³⁵. South Africa has local production preference points in tenders and is in the process of replacing these with a new system where a percentage of designated products will be procured only from domestic producers. Procurement preferences legislation is in place in a number of other countries in Africa but is not always utilized

These examples highlight that some emerging countries have taken active steps to protect and support their pharmaceutical industries. Manufacturers often also benefit from other means of support. In India, it is claimed that producers of final formulations receive substantial government assistance to promote exports including:

- Duty free imports of equipment and raw materials for export products
- Ten year tax holidays if located in Special Economic Zones (SEZs)
- Export credits
- Low utility rates
- Working capital credits
- Enhanced depreciation allowances

The result is that final formulation imports to our continent have benefited from substantial government support in their country of origin and then often do not attract duty. Conversely, African manufacturers frequently have to pay up to 25% tariffs on imported APIs (and other inputs).

This situation is obviously working against local industry. The lack of a level playing field poses a genuine threat to the sustainability of high quality pharmaceutical production in Africa and limits the ability of companies to make the investments required to upgrade their plants. It is imperative that this imbalance is addressed if the enabling environment needed for sustainable high quality production of finished products in Africa is to be achieved. Only in this way will the dire consequences of relying on imported drugs from a quality (and possibly price) perspective be avoided.

³⁴ <http://www.thehindu.com/business/article2366488.ece>

³⁵ Pharma exports to grow 35% this year. <http://www.business-standard.com/india/news/pharma-exports-to-grow-35-this-year/451194/>

In other developing regions and some parts of Africa, protectionist tools such as restricted lists have been used in support of the industry. These lists involve import prohibition on identified products and have been used in countries such as Nigeria and Ghana. According to local actors, these lists have been instrumental in the development of domestic industry. For example, it appears that, until Ghana introduced a restricted list of 13 products, it had five local manufacturers and that today it has 22 active manufacturers. In Algeria and Tunisia, once a locally manufactured generic is registered, the innovator is given two years in which to commence local production. Failure to do this, results in a ban on importation of the finished product and the market can then only be served through locally produced products. This strategy has been important for local industry growth in both these countries where, in addition to government owned laboratories, the market has seen the entry of a number of private sector players in the last ten years.

However, the context in which restricted lists and other protectionist tools are introduced is critical. In considering such steps, it is imperative that public health implications are prioritized. Direct support to industry to take advantage of the opportunities arising provides a chance to upgrade to international standards over a defined period of time and to level the playing field for our manufacturers. Once a critical mass of companies has reached requisite standards, a restricted list can be put in place.

Nonetheless, a recent study published by WHO³⁶ (which supports development of local production of essential medicines) finds that the evidence to link local production to improved access (in terms of the range of dimensions) is ambiguous. Evidence is taken from, for example, India where the emphasis has perhaps been more on developing industry for its export potential than on national public health. This is a cautionary observation since a fundamental objective of the PMPA is improved public health.

This Business Plan is premised on the view that high quality local production will benefit public health across our continent as well as provide economic benefits. For this to be achieved, industrial development tools must be utilized and coordinated with health priorities in a coherent policy and regulatory framework that supports and requires the industry to meet established standards. Chapter Three will elaborate on how a pragmatic and holistic approach can enable companies to continue to operate and have improved access to factors needed to upgrade whilst risk to public health from short term non-GMP standards of production is minimized.

2.2.8 Supporting industries and associated infrastructure

Well developed related and supporting industries and infrastructure are crucial for the pharmaceutical sector. The supporting functions encompass the creation of the appropriate scientific and knowledge base and include educational and training institutions; laboratories and research institutes involved in preclinical and clinical testing (clinical research organisations and research labs); suppliers of all manufacturing equipment and inputs; as well as a sound logistical system for distributing both inputs and the finished products. Other supportive infrastructure includes legal and financial systems; developed information and communications technology (ICT); and a reliable and affordable supply of utilities.

Lack of related and supporting industries poses significant challenges for the African pharmaceutical sector. For example:

³⁶ Local Production for Access to Medical Products: Developing a Framework to Improve Public Health. WHO publication. 2011.

- Whilst in some member states there are world-class research facilities, the majority of African states lack clinical research organisations and bioequivalence centres. As a consequence, companies have to seek out these services globally (many products currently on the market have not been through such studies or provided similar evidence – e.g. biowaiver)
- Distribution chains are fragmented and grossly inefficient with as many as 724 licensed medical distributors in Nigeria³⁷, over 200 in Zimbabwe³⁸ and 296 in Sudan and South Sudan³⁹
- Utilities are unreliable and prohibitively expensive and supply interruptions are a regular occurrence
- The financial and legal infrastructure in the majority of African countries is not supportive of the development of African pharma
- Specialised skills and know-how are required in areas including tooling and fabrication, clinical research, instrumentation and equipment calibration to name but a few. The absence of these skills in some markets results in a situation where local companies often incur additional and unavoidable costs for the maintenance of advanced technologies because they have to fly in experts from abroad
- The lack of a reliable supply of market intelligence services is also problematic as it limits manufacturers' ability to make decisions on product choice, portfolio optimisation and production and supply chain planning. Investors have cited a lack of credible market data as being an important issue that limits their enthusiasm for the sector

2.2.9 Skilled human resources

The pharmaceutical manufacturing system requires specialized skills in a number of disciplines, including pharmacy, chemistry (analytical, organic, synthetic, medicinal), the biological sciences (biochemistry, microbiology, molecular biology), engineering (mechanical, electrical, chemical, industrial, process), the life sciences (medicine, pharmacology, toxicology), and management (strategy, financial and management accounting, operations, logistics, commercial law, etc.) and Information and Communications Technology. The current training and education landscape consists of various providers with the key partners being traditional universities which offer various science, engineering and technology degrees. These degrees are relevant only to the extent of providing solid grounding in scientific theory which is crucial for industry. However, they lack industry applicability and practicality. Therefore, a chemistry graduate will still need industry-specific training to gain the skills which will render him/her productive in a manufacturing environment.

Stakeholders report, for example, that it takes up to three years to train a new recruit who has a basic qualification in the various relevant disciplines and to convert him/her into a skilled pharmaceutical operator. This is not uncommon and experience from around the world shows that there are a number of institutions that offer training to bridge such a gap. Stakeholders also report that the lack of available skilled human resources across the broad array of disciplines identified above is a major constraint and that the resources and

³⁷ IFC

³⁸ Personal communication with pharmaceutical executives

³⁹ WHO

expertise needed to enhance the skills of workers across the industry system are insufficient. Furthermore, there is limited access to the know-how required to implement international GMP. A number of companies who have sought guidance from international consulting firms have found that guidance to be, at times, of questionable value and often prohibitively expensive.

There are a number of ongoing initiatives aimed at increasing the supply of skilled human resources for the pharmaceutical manufacturing system. They include:

- WHO's Essential Medicines Group which organizes ongoing training activities in support of the industry as well as capacity building for regulators
- USP, which has been working with a number of regulators to enhance post marketing surveillance capabilities and has also developed a set of modules for training in different technical aspects of production that could be developed for and rolled out in Africa
- The collaboration between Saint Luke Foundation in Tanzania and Howard and Purdue Universities in the US. This collaboration has already established a valuable model for the training of industry actors and regulators at the Foundation's industrial pharmacy training centre in Moshi, Tanzania
- Various African universities and research institutes involved in training science undergraduates
- Other Non-Governmental Organisations, such as Action Medeor, which run courses on various aspects of the disciplines involved in pharmaceutical manufacturing

These and other worthy initiatives need to be built upon so that the requisite skills for the sector can be developed and models from other continents adopted in a concerted and comprehensive approach. In other geographies, there are specialized training institutions which offer programmes specific to the pharmaceutical industry across many of the requisite skills. Examples include institutions like Purdue University and Stephens Institute of Technology in the United States and the National Institute for Pharmaceutical Education and Research (NIPER) in India.

The Saint Luke Foundation/Kilimanjaro School of Pharmacy and Muhimbili University in Tanzania are examples of specialized centres in Africa that have demonstrated a valuable model for the training of industry actors. Expanding this and strengthening other entities with the potential to provide specialist training is critical to the long term sustainability and viability of the industry on the continent.

2.2.10 Access to finance

Access to affordable investment capital is regularly identified by the industry as a key challenge that limits its ability to make requisite investment in upgrading to international GMP standards. In 2011, UNIDO conducted some research into the capital requirements of companies and the availability of different types of funding. The options covered included traditional bank debt financing, various types of equity financing, and the opportunity for accessing finance from international sources (including the well developed financial community in South Africa and Development Finance Institutions (DFIs) based in the developed world).

From a demand perspective, most companies in SSA (outside South Africa) wanting to invest in upgrading facilities required long term capital (5+ years) to the tune of multi-million dollar sums (specific cases vary dramatically but typically US\$5mn as a bare minimum).

This research established that traditional bank debt financing was problematic given the high interest rates involved (15% to 30+% depending on the country for local currency denominated loans). An added deterrent, which made such approaches unattractive in the current context, was the risk of dollar-denominated debt, appreciating against the local currency. It also found that loans in excess of US\$3mn were rarely available and that the term was usually less than five years.

However, there are alternative sources of funds available (to a greater or lesser extent), including:

- Local private equity (PE) and venture capital (VC) investors
- Some (though very limited) Initial Public Offerings (IPOs) on certain national stock exchanges
- International private equity and venture capital investors
- DFIs
- Not-for-profit international organizations (both generalists and healthcare focused)
- Pharmaceutical collaborative (technical) partners (including capital injection aspect through to overall deal structure)

Nonetheless, these entities identified various concerns that limit their appetite for the domestic pharmaceutical industry, including corporate culture, exit opportunities for equity investors, and general pharmaceutical industry considerations.

Corporate culture

With regard to corporate culture, the issues most commonly cited included:

- Businesses generally controlled by one shareholder or family
- Focus on retaining the business to pass on within the family
- Reluctance to view exits such as M & A (Mergers and Acquisitions) or a stock market listing positively
- Poor corporate governance
- Poor record and account keeping, lack of audited accounts and other records
- Poorly functioning Boards of Directors – lack of outside independent business experts
- Poor planning; lack of long term strategy and vision

- Personnel issues (e.g. family-owned companies hesitant to recruit external senior management)

Exits for equity investors

For equity investors, the exit options are of concern. The most likely are:

- Initial Public Offering (IPO)
- Trade sale/M & A
- Buy-back by majority shareholder of equity stake
- Purchase of shares by strategic financial investor (e.g. larger private equity group)

The IPO market is often limited due to both immature public markets and aversion of companies to seek a listing. In view of this, an IPO is often not high on any investor's list as an exit strategy. M & A opportunities are also often limited although, with time, increasing demand, and evolving business models and management culture, this may change.

Given the current dynamic and limited opportunities for IPO and M & A, some venture capital groups structure their exit into the initial investment agreement, aiming to allow the investment to match both their requirements and to appeal to family shareholders by using, for example, call and/or put options (i.e. share buy-back clauses) and by defining upfront exactly what growth and increase in value is required. In other words, this share buy-back structure entails purchase of the venture fund's stake by the major shareholder – generally the controlling family – at a pre-agreed price premium.

This creative deal structuring addresses the exit issues inherent in the local market. Importantly, it also addresses a key concern of family-owned businesses who want to retain long-term ownership within a tight circle of shareholders since it gives them the ability to buy out the investor. However, a negative aspect of this structure is that, should the major shareholders not be in a position to buy back the shares, there are likely to be contractually agreed penalties enforced by the investor.

The final option, purchase of the share stake by a new private equity investor, is currently relatively unlikely. However, with improved market conditions and the increasing attractiveness of local manufacturers, such exits may be more likely with time, especially when international PE houses acquire stakes in these companies as a means of rapid expansion into sub-Saharan Africa.

Pharmaceutical industry concerns

The industry specific issues most often raised included:

- Need to recruit specialized, highly trained staff and the limited local availability
- Inability to manufacture quality products that are competitive with subsidized imports

- Lack of accurate, comprehensive market data, analysis and forecasts
- Weak regulation and consequent penetration of sub-standard and counterfeit products which then erode the market

Overall implications for accessing capital

Sources of equity do exist and could be accessed by the different industry players although no one capital structure or source of funding will be appropriate for all players. The observations from this work are that an improved market context and evolving financial systems will increase options. However, it is also clear that direct government intervention in addressing the weaknesses of the pharmaceutical system will be an important factor that encourages all forms of investor to show greater enthusiasm for the industry. It would also be helpful if international entities such as the IFC were to review their current policies on investment in the sector in Africa (e.g. requirement for WHO prequalification). Such policies hinder them in fulfilling a role in supporting the development of high quality manufacturing of essential medicines on our continent with the associated health and economic benefits.

2.2.1 | Status of intra Africa trade in pharmaceuticals

The ability to access regional markets depends on a number of factors, including competitiveness, product portfolio, product quality and price, as well as the ability to meet the regulatory requirements and processes of regional NMRAs. Market penetration and access also reflect the ability to adapt to different circumstances and speak to the need to revise and amend business models, form partnerships and do what is necessary to succeed in other markets. Access to markets is also reliant on the sector having efficient internal regulatory processes, effective supply chains and willing buyers.

It is generally difficult for local manufacturers to access external markets because of potential buyers' perception that their products may be of poor quality and the general lack of faith in the competencies of other regulatory agencies. Furthermore, registration delays and the peculiarities of regulatory frameworks in external markets are problematic. Improved trade among our countries in the realm of pharmaceuticals is dependent on increasing the links between our companies and on supporting local industry to compete with imports in the short term whilst it evolves to a point of long term sustainability.

Data on trade in pharmaceutical products among our member states is limited, mainly because the official trade statistics are not sufficiently disaggregated to allow the precise identification of most pharmaceuticals. However, it is often quoted that 30% of pharmaceuticals used in Africa are made on the continent, suggesting that there is significant room for expansion. Outside the donor funded markets, the regulation of imports from other continents is extremely problematic. Consequently, increasing market share of products manufactured under close scrutiny by our NMRAs through increased intra Africa trade in pharmaceuticals will contribute to improved access to quality, affordable essential medicines.

2.2.12 International development assistance for local production

Our development partners have, until recently, adopted different stances on the importance and imperative of strengthening local production of essential medicines. Now, however, the general consensus is shifting towards our own position, which was publicly formalized in 2005. Yet, despite this historical lack of consensus, many initiatives have already been taken by the international community to support local production or in support of our health systems (e.g. through improving pharmaco-vigilance). Actors have included multilateral organisations, bilateral arrangements between countries, universities, and non-governmental organisations. The areas of intervention have included regulatory capacity strengthening, regulatory harmonization, skills development, and technology transfer.

However, despite concerted efforts on many fronts, we have still not seen the hoped for development of the sector. In part, this may be due to lack of coordination among initiatives, a somewhat inevitable consequence of different institutional priorities, mandates and time perspectives. Now that we have developed the PMPA Business Plan, this will provide a central function to facilitate coordination and cooperation so that there is a genuine impact on improving health outcomes (and associated economic benefits) through developing the local pharmaceutical industry.

2.3 CHALLENGES AND OPPORTUNITIES FOR LOCAL PRODUCTION

The previous section described the current status of the pharmaceutical manufacturing system across our continent. It highlighted the diverse contexts but also embarked on identifying some general trends and issues that represent both challenges and opportunities for the sector if it is to deliver on the vision of high quality, affordable essential medicines and associated economic benefits. Here, we lay out the specific challenges and opportunities faced by the industry.

2.3.1 Challenges of achieving universal GMP

As demonstrated, achieving GMP standards is technically possible across our continent but genuine challenges face the industry if companies are to reach and maintain this level.

In general, these challenges can be broken down into technical considerations regarding the expertise needed in setting up and running high quality plants; financial considerations, such as mobilizing investment capital; achieving and maintaining competitiveness given the cost implications of setting up and running a GMP compliant facility; and infrastructure to assist local production, such as access to bioequivalence facilities and other supporting industries.

The current situation on many of these issues has already been described and a summary of key challenges as perceived by the industry is now given in Table 2. However, pharmaceutical manufacturing companies currently display a wide range of attitudes. They include companies that have already demonstrated their commitment to international standards and achieved them; those who are currently in the process of upgrading their operations; companies who aspire to improved quality but have so far not been able to mobilize the necessary range of expertise and resources; and those that are happy to continue producing at standards significantly below GMP.

Table 2: Key challenges identified by the pharmaceutical sector in achieving universal GMP standards

<i>Technical Expertise</i>	<i>Financial Considerations</i>	<i>Infrastructure Requirements</i>
<ul style="list-style-type: none"> • Access to know-how for designing, upgrading to and running GMP compliant facilities • Access to skilled human resources such as industrial pharmacists, microbiologists and analytical chemists 	<ul style="list-style-type: none"> • Access to affordable investment capital • Policy incoherence (e.g. tax on inputs versus tax free importation of finished products, restricted lists, capital controls, etc.) • Market context (e.g. penetration of counterfeits, uneven playing field versus imports – to some extent a function of policy incoherence) • Variability in quality amongst market players • Access to export markets and their current fragmented nature • Competitive production given cost structure (function of efficiency) 	<ul style="list-style-type: none"> • Reliable utilities (implications for cost as well as compliance with GMP) • Access to bioequivalence centres • Regulatory oversight (impact on access to capital and market context considerations) • Underdeveloped supporting industries (implications for cost and quality) • Lack of market data (implications for strategic planning and access to capital) • Uncoordinated and/or vertical approaches to developing the sector

Depending on where companies are positioned along the production chain, from very low to international standards, unsurprisingly, they have differing views on the challenges they face and their ability to reach and maintain competitive production to international standards. For those that have achieved the mark, or are well on their way to it, concerns relate to sustainability as technical challenges have already been addressed. For example, leading manufacturers cite limited regulation of the market as a key challenge given that they have to compete with firms with lower standards and therefore a lower cost base. For others, there are concerns that the sector’s reputation for variable quality standards could limit the opportunity for exports and even create a preference in their domestic market for international products. They also cite ‘unfair’ competition from companies overseas who benefit from significant government support and may also be manufacturing to standards below their own.

Furthermore, the lack of coherence in policies previously described is also a cause for concern given the advantage that imports often enjoy. Companies that aspire to manufacture to international standards also cite lack of regulatory oversight as an important barrier. This is one of the issues identified by investors as currently limiting their enthusiasm for the industry in many countries. Pharma companies often also cite the challenges in accessing the necessary know-how to implement upgrading programmes. However, for some companies, these barriers and the lack of regulatory enforcement mean that they neither need nor aspire to improve production standards.

2.3.2 Specific opportunities for strengthening local production of medicines

This sub-section describes three particular areas - utilizing the TRIPS flexibilities; synergies with R & D initiatives; and greater linkages between manufacturers as well as other actors – from which local pharmaceutical manufacturing could benefit in order to become a critical public health asset for the continent.

Intellectual property rights and full use of TRIPS flexibilities

Many African countries belong to the World Intellectual Property Organization (WIPO) and the World Trade Organization (WTO) and consequently observe international norms and standards with respect to Trade-related aspects of Intellectual Property Rights (TRIPS). Protection of such rights is enshrined in national legislation and, in cases of infringement, intellectual property right holders can seek relief from courts and assert their rights in cases of patent, trademark and copyright infringements. Most African countries enjoy the early working provision (Bolar) that allows companies to research and develop a product before patent expiry. Further, there are no data exclusivity (DE) provisions and no supplementary protection certificates (SPCs).

Thus, market entry in non-LDC Africa can occur immediately upon patent expiry. However, despite these provisions and largely because of small markets and delays in medicine registrations, many international companies rarely register patents in African jurisdictions or launch generic equivalents already developed ahead of later patent expiries in Europe and North America. Because many countries on the continent are classified as Least Developed (LDCs), in line with WTO rules, they have until January 2016 to comply fully with the TRIPS provisions. Furthermore, there is a strong possibility that the 2016 deadline may be extended. The TRIPS flexibilities include the following:

- Exemptions from patentability (Article 27.1, 27.3)
- Provisions to issue compulsory licences and authorize parallel imports (Article 31)
- Exhaustion of rights (Article 6)
- Limitations on data protection (Article 39.3)
- Bolar provision or early working (Article 30)

Article 31 grants governments the right to license third parties to use patents without the consent of the rights holder if it is in the public interest; in cases of national emergency; if there is failure by the rights holder to exploit the patent or there is insufficient working; and, lastly, as a remedy to anti-competitive practices. This provision is mainly for the supply of the local market but it does not preclude use for exports to LDCs without any manufacturing capacity. It was introduced following the adoption of Paragraph 6 of 2003 which waived the requirement of Article 31(f) of TRIPS which stipulated that compulsory licences (CLs) could only be issued for domestic use and was in recognition of the fact that many LDCs that needed to make use of the flexibilities had no domestic manufacturing capacity. Lastly, it is important to emphasize that Article 31 is not intended for use only in emergencies and is not limited to certain diseases.

For various reasons, only a few member states have exploited the flexibilities. One of the most important reasons is that many LDCs have not incorporated the flexibilities into their national legislation as they are required to do prior to exploitation of the provisions. In fact, a review of many LDCs' intellectual property laws reveals that they not only fully comply with the WTO's Trade-related aspects of Intellectual Property Rights (TRIPS) agreement but, in some cases, far exceed the protections of intellectual property rights expected of them (TRIPS+).

Other reasons why LDCs and other African countries (with productive capacity) have not taken advantage of the TRIPS flexibilities include:

- A lack of political will to enact the necessary amendments to intellectual property rights law to enable countries to exploit the flexibilities
- A general lack of knowledge among the technocrats tasked with dealing with IPR and access to medicine issues about the flexibilities and how to go about creating an enabling environment; and, finally
- Capacity constraints such as weak legal and regulatory frameworks and weak supporting technical know-how and administrative capacity which remove any incentive or inclination to act on the flexibilities

Africa therefore faces a simple choice in the next four years - to fully exploit the TRIPS flexibilities and accelerate the ongoing negotiations for an extension to the 2016 transition period or face the prospect of paying more for drugs in the future. The global economic crisis has seen the scaling down of treatment programmes and the cancellation of Round 11 of the Global Fund. It is clear that in the long term the sustainability of treatment regimes in Africa may well depend on the ability to fully utilize the flexibilities and to develop the competencies to make our own medicines. Chapter Three of this document will propose how the Business Plan can endeavour to facilitate the utilization of these flexibilities for the benefit of the peoples of the continent and for local manufacturers who are international GMP compliant.

Research and development

Africa lags behind other regions of the world when it comes to innovation and knowledge creation. In 2002, the continent spent just 0.3% of GDP on R & D versus the global average of 1.7% and had only 1.2% of the world's researchers⁴⁰. The Organisation for Economic Co-operation and Development (OECD) refers to research and development (R & D) as the "creative work undertaken on a systematic basis in order to increase the stock of knowledge, including knowledge of man, culture and society, and the use of this stock of knowledge to devise new applications"⁴¹.

R & D activities broadly cover three areas of activity: basic research, applied research, and experimental development, all with the sole intention of discovering and generating new knowledge and products and ultimately providing solutions to problems.

The capabilities needed for R & D are important for innovation and the discovery of new products, for reverse engineering current products, and for creating new formulations and

⁴⁰ A World of SCIENCE, Vol. 2, No. 1, January–March 2004

⁴¹ OECD definition

delivery systems. The shortage of researchers on the continent is exacerbated by the loss of skills to the developing world. For example, it is estimated that more than a third of practising highly skilled African scientists are now living in the developed world⁴².

However, the situation is changing, with greater emphasis now being put on R & D and with the formation of key institutions like the African Network for Drugs and Diagnostics Innovation (ANDI). At continent level, the need to promote research and development is reflected in a number of documents, including:

- Africa Health Strategy 2007-2015
- Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (WHA 61.21 of May 2008), a WHO document
- Abuja Declaration of March 2006
- Accra Declaration on Health Research of June 2006; and
- Algerian Declaration on Research for Health in the African Region of June 2008

Furthermore, various countries have national research strategies and are investing significant resources to scale up R & D. Government owned institutions and medical research institutes now have active medicinal and drug discovery programmes and some leading teaching institutions have also created drug discovery and development programmes, as well as clinical trial centres which can be used for bioequivalence testing.

Local pharmaceutical companies on the other hand are not involved in any original R & D work. A few companies do have research and development programmes but most have only small formulation departments where reverse engineering of marketed medicines is done. Innovator companies that are active on the continent do not undertake any direct original research work in Africa although they outsource some parts of the development work to institutions on the continent and spend considerable resources on clinical trials for new chemical entities.

The PMPA and other African imperatives recognize the critical importance of original and basic research (drug discovery and development) and its overall strategic importance to the future and long term viability of the industry on the continent. However, for the purposes of this Business Plan, R & D is used broadly to refer to experimental development which entails the use of existing scientific, technological and other knowledge and skills in order to produce modified or improved products, processes and services. This is particularly relevant to the creation of new formulations, delivery systems, combination products and paediatric formulations, areas in which African manufacturers are far behind their counterparts in other developing countries.

Nonetheless, novel R & D should become an increasingly important focus area for our continent and competencies in this field will have to be built up significantly. This need is evidenced by the fact that less than one per cent of all the thousands of new chemical entities developed in the last 30 years are for treating the neglected diseases which predominantly affect Africa⁴³. Consequently, organisations like ANDI need to be supported in their work so

⁴² Joint Statement by the Network of African Science Academies. July 2009 - www.nationalacademies.org/includes/NA-SACbrainrain09.pdf (accessed December 2011)

⁴³ Pierre Chirac, Els Torreale. Global framework on essential health R & D. *The Lancet* Vol. 367 May 13 2006

that they can respond to the needs of the continent for effective medicines for the diseases that plague us. Furthermore, ANDI has set up a network of 32 centres of excellence across Africa involved in drug discovery, pre-clinical and clinical work.

The AUC believes that our continent should tap these skills sets and competencies to respond to the needs of industry for innovative formulations, improved delivery systems and paediatric formulations among others. Consequently, the AUC will, in partnership with ANDI and others, seek to fast track the development of technologies and the speedy diffusion of these technologies to international-GMP-compliant African manufacturers.

There are a number of research partnerships between African and international organisations and they include:

- The National Research Foundation of South Africa/Emory University/SCYNEXIS Advanced Drug Discovery Program
- The Drugs for Neglected Diseases initiative's (DNDi) clinical research platforms: Leishmaniasis East Africa Platform (LEAP) in Kenya, Ethiopia, Sudan, and Uganda; and the Human African Trypanosomiasis (HAT) Platform based in the Democratic Republic of Congo (DRC) for fighting sleeping sickness
- The Medicines for Malaria Venture (MMV) network of clinical trial sites in malaria-endemic countries

These partnerships need to be encouraged and accelerated and the AUC is keen to engage with them and others to explore how work under the PMPA can assist in making new products widely available.

Partnerships, collaboration and improved business linkages

Partnerships and collaboration between industry and various players such as R & D institutions, education and training providers are critical for the growth of the industry. Moreover, partnerships between manufacturers themselves are needed to realize economies in product development, raw material procurement, equipment servicing and maintenance among others. In our industry, the practice of partnering is not well entrenched. Table 3 reviews the current status of such partnerships which are critical for the growth of the industry and for increased access to medicines.

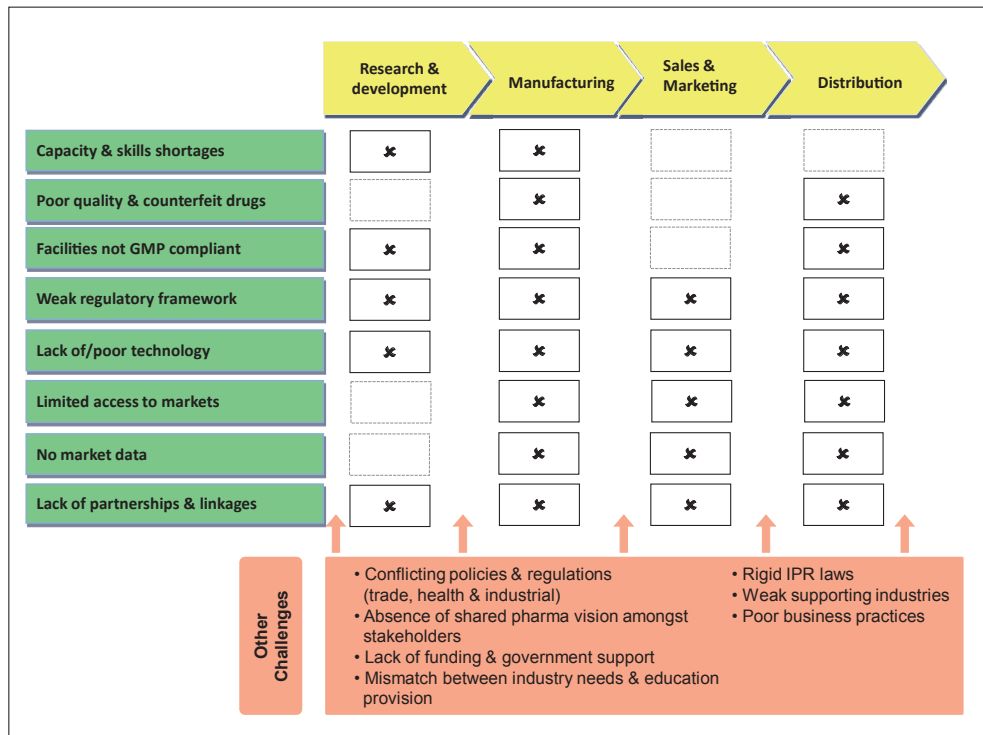
The current limited number of relationships between regional and international entities represents an opportunity for the sector. Facilitating partnerships between companies on our continent, as well as with international firms, could enable access to various industry needs including know-how, enhanced product portfolios and investment capital. There is also the potential to strengthen relationships between the corporate sector and academia on the continent and via Product Development Partnerships (PDPs) among others.

Table 3: Status of partnerships impacting on the pharmaceutical sector in Africa

Partnership type	Functions	Status
R & D partnerships between industry, universities and research institutes	Important for innovation, discovery, development and commercialisation of new products and new generic formulation and delivery systems	Non existent ANDI seeks to fill this space
Technology transfer partnerships between local companies and external partners	Important for the introduction of new technologies and products quickly and to significantly reduce development costs and time to market in the case of generics	A few examples: <ul style="list-style-type: none"> • Cipla and Quality Chemicals (Uganda) • Zydus Cadila and Almeta Impex (Ethiopia) • Aspen GSK (RSA) • Sanofi Pasteur and The Biovac Institute (RSA)
Education and training provision partnerships between industry and institutions of higher learning	For the provision of adequate training and education relevant to the skills requirements of the pharmaceutical industry	Scarce: <ul style="list-style-type: none"> • Muhimbili University (TZ) • Saint Luke Foundation (TZ)
Partnerships between development partners	For coordinated and integrated support responsive to the needs of industry	Present: <ul style="list-style-type: none"> • WHO & USP • UN organizations (UNIDO, UNCTAD, UNDP, WHO, World Bank) • UNIDO,
Cooperation between industry and various stakeholders in government	For the creation of an enabling and supportive environment as well as a shared vision for the industry	Weak – a lot of work needs to be done
Business linkages between local, regional and international companies	This is for technology transfer, access to new products and foreign direct investment into the local pharmaceutical sector	Multiple agencies and product or distribution licensing agreements

2.4 SUMMARY OF CHAPTER 2

Figure 6: Illustration of challenges across the manufacturing value chain



Key messages from Chapter Two include:

- Pharmaceutical manufacturing occurs within a complex system with a wide range of stakeholders
- The status of the ‘pharmaceutical manufacturing system’ in those of our countries where manufacturing occurs is unique
- The current status of manufacturing activities on our continent varies dramatically across countries
- In North Africa and RSA a broad range of products are manufactured but in most of SSA product portfolios are generally limited
- There are few internationally certified (WHO prequalification or approval by a ‘stringent’ regulator) manufacturers for products against HIV and malaria
- Most inputs are imported, with an estimated 95% of APIs coming from overseas, largely from India and China
- It has been demonstrated that production to international standards is possible on our continent
- However, the quality standards to which companies on our continent produce vary both across different countries and regions and also within individual countries

- Companies have a wide range of perspectives with regard to upgrading production standards
- The issue of sub-standard products has grave implications for public health; we therefore need to take steps to increase quality standards across the board
- Concerns exist as to whether international standard production can be competitive on our continent
- Research and real world insights show that the economics of pharmaceutical production are complex (and go beyond traditional notions of economies of scale) and are impacted by efficiency of production
- Simulation exercises and insights from leading companies show that high quality production can be competitive with imports from India if there is a more level playing field (from a policy perspective) and if efficiencies in production can be realized
- The level of regulatory oversight in many countries is insufficient
- The policy and legislative landscape in most countries is not supportive of local industry and often confers a disadvantage versus imports of finished formulations from countries which provide significant support to their sectors
- The sustainability of high quality local production will benefit from development of supportive industries and associated infrastructure
- The different activities across the manufacturing system require significant skilled human resources and know-how but current availability is limited
- Access to finance is a challenge for many industry players given that long term bank debt of the order of magnitude required is often not available and the appetite of equity investors for the sector is somewhat limited
- Intra Africa trade in pharmaceuticals is limited due to various obstacles from a regulatory perspective as well as the reluctance of companies to work together. There is a substantial opportunity for increased trade in high quality essential medicines and for this to lead to improved health outcomes
- There are a number of untapped opportunities that could assist the industry and enable it to become an important public health asset. These include full utilization of the TRIPS flexibilities, the output from the increasing focus on novel R & D, and facilitating business linkages and partnerships with multiple aims, including accessing new products, investment capital and know-how

3. SOLUTIONS

Chapter One of this Business Plan dealt with the challenges that impact on the delivery of quality healthcare on the African continent and presented current estimates and projections of future disease patterns, as well as forecasts for the economic outlook for Africa. Chapter Two presented the components and complexity of the pharmaceutical manufacturing system and identified the wide variety of contexts across our continent. It also outlined the challenges across different dimensions of the system. Figure 7 below is a schematic representation of the key aspects of the system that need to be tackled if the industry is to respond to the continent's ambition to achieve self reliance and sustainability in the provision of safe, affordable, efficacious medicines.

Figure 7: Illustration of foundations required, key interventions and ultimate ambition for the Business Plan



The PMPA Business Plan puts forward an approach through which technical assistance can be provided to member states across the key dimensions of the pharmaceutical manufacturing system so that our companies can respond to Africa's need for a sustainable supply of affordable, safe, efficacious, quality medicines. It identifies the need for TA in non-producing countries in collaboration with other associated initiatives (such as AMRH and the specific activities of different RECs).

In structuring a continent wide plan for the pharmaceutical sector, the heterogeneity of Africa and the different aspirations of our member states in relation to pharmaceutical manufacturing and the need for action at various levels and across a number of dimensions are critical. This Business Plan therefore describes an approach in which solutions to common issues will first be developed at a central level and then tailored to the specifics of the country context.

Implementation of the PMPA will largely take place at the country level although there are also specific aspects of policy and international development assistance that lend themselves to action at the level of the RECs and the continent. Critical to success is the recognition that the pharmaceutical manufacturing system involves a broad array of players and that strengthening the different components requires a similarly broad range of expertise. No one entity contains the necessary insights, capacity, mandate or skills to address the full range of requirements. Consequently, the need for collaboration between different parties is of paramount importance. In view of this, building a consortium of partners is recommended and the AUC will provide the central authority under which these parties can work together. Further details of the nature of the envisaged consortium and how it will function are described in more detail in Chapter Four.

3.1 THE GENERIC SOLUTIONS PACKAGE

Figure 8: Schematic indicating the interdependence of critical aspects of the system

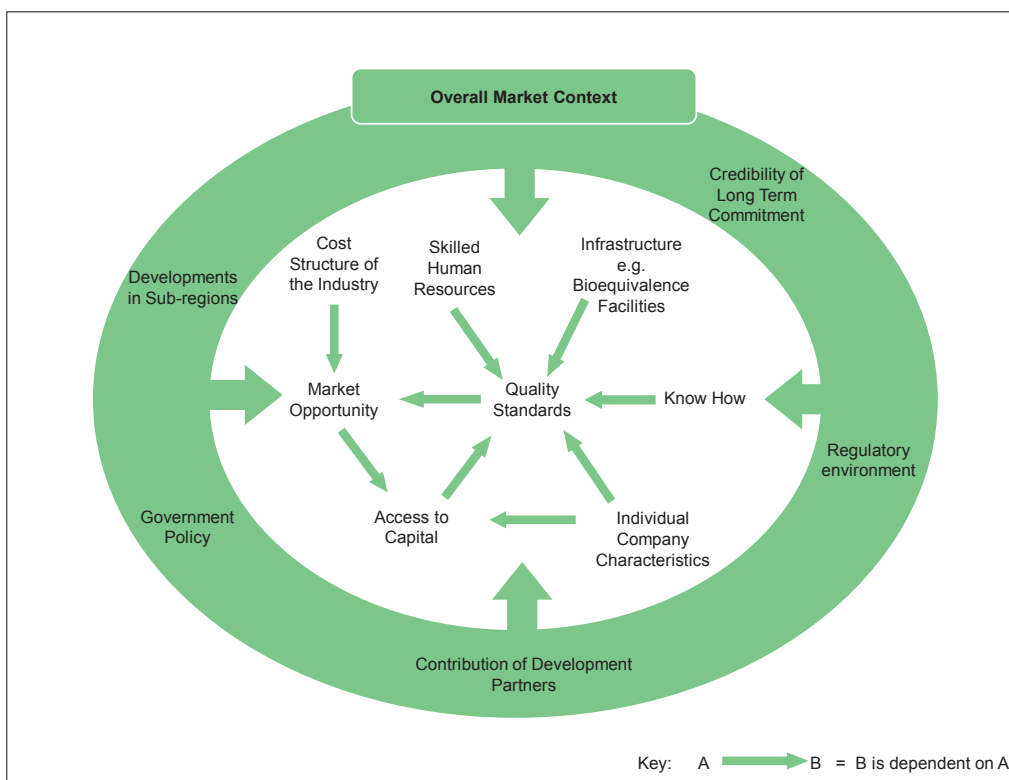


Figure 8 illustrates the interconnectedness of key dimensions and requirements of the manufacturing system. It is a schematic simplification that provides some examples of how issues are connected. The specifics in each context differ depending on numerous variables, including current status, ambition, level of development and access to capital markets, status and capacity of the regulator and more.

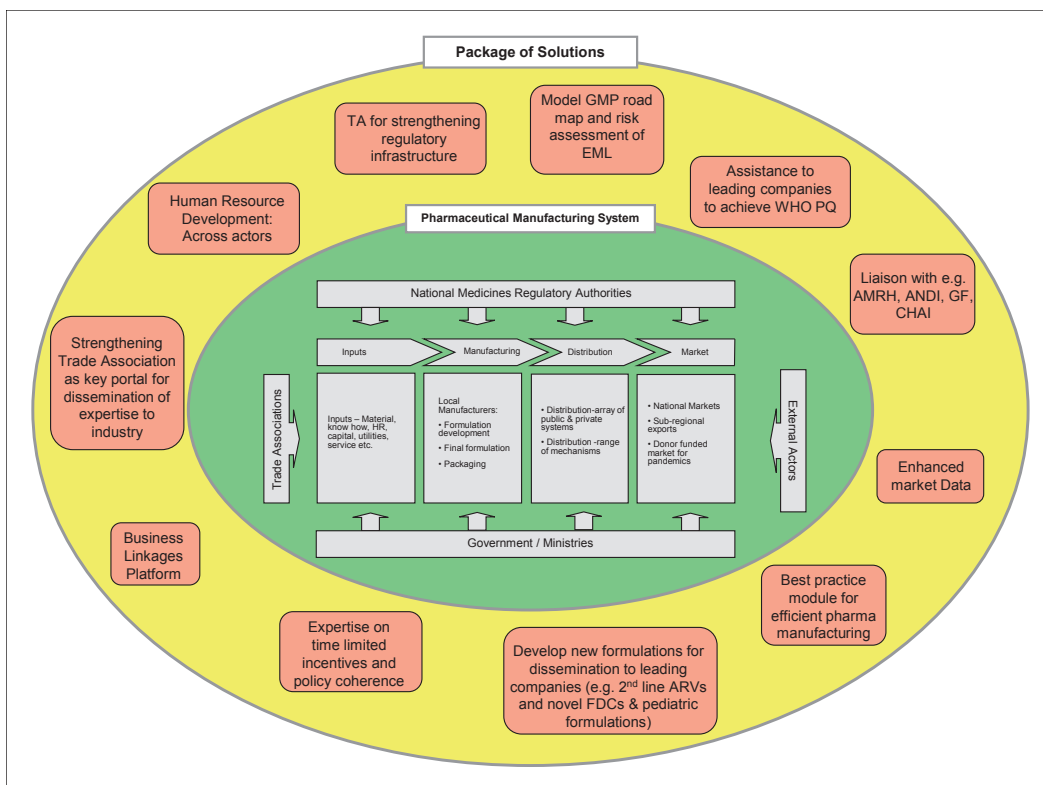
The generic solutions will constitute a central repository of expertise, knowledge, skills and capacity which can be accessed and tailored to the various contexts. This section will focus on a description of the solutions package, building on existing interventions and expertise. In the context of the PMPA, new tools and approaches will be developed that can be

implemented with genuine collaboration between partners. The generic solutions package includes:

- Development of Human Capital
- Development of a GMP road map in conjunction with a risk assessment of the Essential Medicines List
- Insights and guidance on time limited incentive options which governments can employ to support industry given the specific country context as well as identification of non-fiscal support such as facilitating access to know-how
- Recommendations and advocacy to facilitate access to affordable long term investment capital of sufficient magnitude to enable upgrading of facilities to international standards
- Insights into legislative and policy requirements, tools and options for development of the local pharmaceutical sector and an understanding of which issues are to be dealt with at country level and where regional level coordination/negotiation is involved
- Technical assistance to regulators to identify critical regulatory functions on which they should focus (not just in the context of the PMPA but also in assuring product quality in the market place) and to develop and implement an organisational development plan for achieving these objectives
- A partnership or business linkages platform which could cover an array of different relationships, including those that provide access to capital and/or technology and know-how
- Working with centres of excellence to develop formulations to take advantage of the TRIPS flexibilities and to assist companies that have reached GMP standards to access affordable high quality dossiers for established generic products that have significant public health importance
- Development of new formulations for transfer to international GMP compliant manufacturers
- Guidance for strengthening national and regional pharmaceutical manufacturers' associations
- Developing options and recommendations for improved market data collection and availability

The range of the solutions package is shown in Figure 9 below and a proposed mechanism by which a tailored approach for each country context can be developed is also described below.

Figure 9: Indicative package of solutions to address the wide ranging issues involved



3.1.1 Human resource development

One of the most critical aspects of the long term sustainability of the pharmaceutical industry on our continent is developing the human resources necessary to fulfil the different functions within the pharmaceutical manufacturing system. Historically, there have been many worthy initiatives to develop skills. However, they have been uncoordinated and have not had the impact they could have had had the HR requirements for different aspects of the system been developed in a deliberate and considered way. The system requires enhanced human capital in regulatory functions, technical aspects of manufacturing, business and management aspects of manufacturing, and in the policy making sphere across different ministries.

There are various mechanisms available for building the skills of those already involved in the sector and there is a need to increase the availability of skilled professionals for long term sustainability to be achieved. In view of this, the human resource development component of this Business Plan identifies both formal academic training of sector participants at centres of excellence and a structured set of modules to be made available to industry actors at individual country and/or country cluster levels. The importance of the country/cluster level training cannot be overestimated. The progress of the industry requires not only the dry technical skills involved but also a shift in industry culture across the system such that quality and efficiency become concepts embedded within the psyche of all practitioners.

At the enterprise level, those companies that have reached international standards have repeatedly emphasized the need to adjust the internal culture of the company and have utilized many mechanisms to do this. Experts in efficient manufacturing also emphasize

the need for efficiency to be part of a company's core culture for continuing improvements which lead to evermore competitive production. Best practice in terms of enterprise level training programmes will be developed and disseminated to companies through trade associations. Companies themselves will be responsible for taking advantage of such materials but sector level training will also be conducted as part of the PMPA. This will form a basis from which enterprise level initiatives can be designed and implemented.

It is also necessary to recognize that, for the sector to embark on a new trajectory, we will need to augment our current human resources through accessing know-how in the short to medium term via various mechanisms. For example, the Partnership and Business Linkages Platform described later would provide a mechanism through which companies could engage partners to assist in areas such as plant design. There are many skilled people in other parts of the world whose expertise could be brought in and those in the Diaspora could be encouraged to return.

For example, there are thousands of highly skilled pharmaceutical personnel currently unemployed following the large scale retrenchments by multinational pharmaceutical companies during the global recession. Pharmalot estimates the number of people retrenched at 19,076 in 2011, 53,636 in 2010, 61,109 in 2009, and 43,014 in 2008. Means by which governments could consider facilitating quick access to such expertise include increasing the quota of expatriate working visas for pharmaceutical companies.

The specialized skills sets required to support local manufacturing are described in Chapter Two where there is also a non-exhaustive list of organisations involved in training for the pharmaceutical sector. The AUC, with the assistance of UNIDO, has had initial discussions with WHO, USP, and the Saint Luke Foundation/Kilimanjaro School of Pharmacy about building on their ongoing activities to accelerate human resource development for the industry. Although these entities can assist in the development of human resources already involved in the manufacturing system, the long term supply of skilled graduates who will be vital for sustainability and self reliance in the production of high quality medicines also needs further development. In view of this, the training curricula of schools of pharmacy should be revised so that they incorporate industrial training although this is outside the specific mandate of the PMPA. However, the technical partnership envisaged in the Plan would make experts available to assist those institutions of higher learning that are interested in revising their curricula.

There is also a need to develop further business skills, business culture, and expertise in manufacturing efficiency if the sector is to become sustainable in the long term. Therefore, as well as developing the technical human resources for regulation and production, the consortium will also build on initial insights and establish training modules to provide materials and guidance on which companies can draw to improve their operations and develop business models and structures that are attractive to investors and increasingly competitive in the medium term.

As already pointed out, developing human resources requires different models to develop a strong basis of technical skills and to ensure that this knowledge is then reinforced through continual learning and dissemination to other industry participants. This Business Plan will seek to provide a comprehensive education syllabus through centres of excellence and ongoing training at sector level. It will also be necessary for individual companies to recognize the importance of ongoing training and corporate culture development and to take responsibility for such activities (with sector level guidance from the PMPA).

Technical manufacturing, regulatory and policy skills

Human resource development will involve different levels of intervention by the consortium engaged to do the detailed design and implementation of this Business Plan. At a technical level, training at academic institutions will include:

- A comprehensive syllabus of short term courses for current employees and those aspiring to join the sector. This could initially be conducted at the Saint Luke Foundation (with its partners) and then be subject to expanded roll out as the model is extended (see above). The syllabus would include documentation (drug product/substance, mock drug master file compilation), formulation, design, excipients, coating, bioequivalence, method validation, equipment calibration, filing with the FDA/WHO-PQ (SRAs). Muhimibili University is already offering short courses on these modules as well as courses on validation and qualification, granulation, tableting and coating; quality control of medicines; and coating and sustained release formulations
- A syllabus of pharma-specific long term courses for regulators and industry. The Saint Luke Foundation/Purdue and Howard universities collaboration offers a two year Industrial Pharmacy Advanced Training Programme which will be expanded to other regions of our continent. The focus includes drug development and regulatory quality compliance, drug manufacturing process (GMP), regulatory documents and generic drug approval submissions, and drug discovery. The training is offered in the Industrial Pharmacy Teaching Unit which boasts a fully equipped and GMP compliant production line with 50kg batch size equipment. This programme is based on Purdue University's leading Industrial and Physical Pharmacy Programme

These training courses will be supplemented with the running of in-country/country cluster courses made available to various industry actors. It is imperative that technical knowledge from academic courses is built upon and that there is a structured approach to developing the broad understanding of the range of requirements for high quality production. Equally important is the ability and awareness of all actors of the need to fulfil their particular operational function according to these standards. These in-country/country cluster courses will include:

- A structured approach to building knowledge of GMP and associated processes, practices and requirements
- Specific training aimed at changing the management culture of companies and focusing on quality aspects. As with other courses, this training will be conducted at a sector level although companies requiring specific in-house training will be able to access the AUC panel of vetted experts independently. Mechanisms for assisting countries with limited numbers of manufacturers wishing to access such training will need to be established, for example, via regional cluster approaches. However, the PMPA will seek to develop materials to assist companies in their internal ongoing training programmes around GMP, culture change and the importance of quality to the business
- Specific training for NMRAs over and above academic courses will also be necessary to enable regulators to build on this knowledge and current expertise to enhance their ability to oversee the market (dependent on infrastructure as well as human resources – see below). WHO and USP activities in this space have already been men-

tioned. However, it is recognized that these initiatives need to be enhanced and that development of regulatory skills would benefit from more additional and perhaps more extensive programmes of support. USP and WAHO have, for example, proposed a ‘training of trainers’ approach for the ECOWAS region, where experienced regulators who have retired could mentor individuals and transfer their knowledge to the next generation who should then act as agents for change within their NMRAs. Such a concept could be developed and rolled out to other RECs. Furthermore, many stringent regulatory authorities and related organisations offer training programmes for regulators from developing countries. The PMPA will seek cooperation with organisations such as the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA) and WHO with a view to offering continuous development programmes for participating African NMRAs. Any initiatives in this area will be coordinated with the ongoing approach to training of regulators that is being developed by the AMRH initiative

- Training for policy makers is a key area that needs to be addressed head on to increase the industry specific knowledge of the technocrats tasked with formulating and implementing policies impacting on the pharmaceutical industry. Given the broad array of ministries involved and the number of staff who will have input, whilst discrete external courses may be appropriate for senior government officials, it is anticipated that a series of workshops and seminars to inform policy makers of the reality of the sector, its complexity, its potential for public health benefits and its need for cohesive policy frameworks will be offered at country level. Some leading African universities have been approached and have already indicated a willingness to design and offer the required training. The AUC will also approach other international training institutions and development partners with the requisite know-how to develop and offer such a programme and will endeavour to twin them with the interested African institutions
- Short term courses for engineering teams, artisans and machine operators. It has become clear through interactions with various industry stakeholders that a key challenge confronting manufacturers relates to the shortage of the requisite skills and experience in tooling and fabrication as well as in optimal plant maintenance and operations. The AUC therefore proposes to start a series of short term courses for technical teams in industry in order to disseminate international best practice and to equip companies to be able to service, maintain and repair their own equipment. This is particularly urgent since one of the causes of long downtimes is equipment breakdown which necessitates the importation of skills, normally from abroad. This is a major disruption in continuous plant operations and is costly for many cash strapped companies

Business skills for the pharmaceutical industry

The development and sustainability of the pharmaceutical sector is dependent not only on the technical skills associated with manufacturing but also the business skills of the entrepreneurs and corporate managers involved. Competitiveness is not only a function of a number of structural aspects of the industry or the development of an enabling environment from a policy, regulatory and legislative perspective. It is also dependent on the ability of entrepreneurs and corporate managers to take advantage of opportunities arising and to achieve their business objectives. The inherent skills of successful entrepreneurs, such as

energy, dynamism, and risk taking should not be underestimated. However, these skills can be further enhanced through the teaching of some key dimensions of doing business in the pharmaceutical sector.

There is potential for establishing industry training programmes at institutions of learning which, for example, could replicate the MBA in Pharmaceutical Management offered by institutions like NIPER in India. The need for such programmes has been endorsed by various pharma professionals who identified the following courses as relevant:

- Accounting and Financial Management
- Pharmaceutical Business Environment
- Business Law
- Production and Operations Management in Pharma
- Strategic Management in Pharmaceuticals
- Pharmaceutical Sales Management
- Marketing Management
- Brand Management in Pharmaceuticals
- Logistics and Supply Chain Management for Pharmaceuticals
- Corporate Governance and Board Leadership

It should also be recognized that many entrepreneurs and corporate managers will not have the time to participate in such extensive training. Nonetheless, the need for specific aspects of business management to be disseminated to the industry is urgent since the time needed for moving from initial planning to mobilizing investment and to upgrading established plants or building new plants is substantial. In view of this and to enable companies to take action rapidly, training in the key skills required for the sector's development will be provided, as requested, through entities such as trade associations.

A key component of this training will focus on changing the prevailing business culture and governance practices in the industry. The management and governance culture of African pharmaceutical companies has consistently been identified as one of the major weaknesses of the industry and is a key reason why investors are unwilling to invest in the industry. This is hardly surprising given that the investment community is understandably not keen to invest in businesses where its views may not be heard and where record keeping, governance structures and roles and responsibilities are not well defined. Thus it is imperative to offer a number of modules for executive training and for building the requisite general management skills and expertise.

Improving competitiveness is another key area for business managers. It is clear that achieving efficiencies requires incorporation of efficiency into the corporate culture but managers need to be given the tools with which to identify the opportunity and to effect change within their organisations.

3.1.2 GMP road map and risk assessment of the EML

The ultimate objective of the PMPA is that all production in Africa should adhere to international GMP standards. There are a number of guidelines set out by different regulators and agencies to define what constitutes GMP but the PMPA recommends that WHO GMP, as established in the WHO compendium on quality assurance 2006, should be the target to which all countries aspire.

Where companies are developing new production facilities, it is recommended that countries immediately require WHO GMP standards but, where there already is an established pharmaceutical sector, a trajectory towards GMP requirements needs to be established. In an ideal world, all companies would immediately upgrade their standards to GMP but this is not practical as substantial expertise is required to address all the aspects involved. Moreover, significant investment is often needed, time is required to adjust the corporate culture towards one that has quality as a central tenet, and processes and procedures need to be defined and validated.

These and other factors mean that a pragmatic approach is warranted since most companies will need to make improvements in order to reach GMP standard and they will require various forms of assistance to do this (see section on other solutions involving both technical support and incentives). Firms also need time to implement change whilst continuing to do business. By the same token, most regulators will also have to increase their capacity and capabilities if GMP is to be enforced widely. This, again, will take time and resources.

Recognizing this situation, the Business Plan recommends the establishment of a 'GMP road map'. Initial work with USP has resulted in the development of a prototype assessment tool that seeks to quantify the level of a company's adherence to GMP. This could be used under the authority of the NMRA as part of country level PMPA implementation to assess the level of compliance with GMP of manufacturers operating in a country. The purpose of the assessment would be to establish a baseline from which a GMP road map for the sector can be established. During the set up phase, the AUC, in conjunction with core partners, will develop a generic road map.

The objective for the future is that all companies should be GMP compliant across all product categories. However, as already pointed out, this is neither possible nor practical right now. The implications of sub-standard production vary depending on the product type in terms of implications for health if contaminated, if products are not effective, or if products were to be mislabelled. Therefore, in the interim, it is proposed that those companies that are not at GMP levels should be restricted to manufacturing only products that are deemed to pose a minimal risk in the event of their quality being compromised. To identify products that would pose minimal risk, a technical review of the WHO Essential Medicines List will be conducted (initial discussions with WHO regarding this undertaking have taken place). Such a risk assessment would be used as a basis for NMRAs to determine which products could be produced by which companies (it may be that there would be a number of tiers below the fully GMP compliant status).

Despite the PMPA recommending a pragmatic approach to improving standards over time, the implications of quality should not be underestimated and the GMP road map will include recommended prerequisites for certain product types (even in the minimal risk category) which must be in place before production can start or continue. For example, production of syrups should not be allowed without proper water treatment plants in place. The

risk of anaphylactic shock in people allergic to penicillin means that beta lactam production should always be in a separate facility to other products. Further suggested prerequisites will be recommended as part of the road map.

In summary, where there is an established industry with varied production standards, the Business Plan espouses a pragmatic approach to improving quality standards with the ultimate goal being international GMP standards across the board. This requires a holistic approach where regulatory capacity development, human resource development, access to know-how and incentives/support to industry are coordinated to enable and require companies to adhere to a GMP road map which will:

- Consist of a series of milestones setting out specific components of GMP that companies would need to have in place by a certain point in time. This would be leading towards a point in the future (probably established by the NMRA following consultations) where all components of GMP would need to be in place
- Need to be pragmatic but also identify critical issues of GMP that should be addressed as an imperative at the outset
- Differentiate between the different GMP requirements for different dosage forms and certain product categories
- Need to be pragmatic, as certain aspects will take some time to implement (e.g. where construction and/or capital mobilization is required)
- Be implemented in conjunction with a risk assessment of the EML whereby companies operating below GMP standards would be limited to production of those products that represent the minimum risk

3.1.3 Insights and guidance on time limited incentives to support industry

A key objective of the PMPA is that international standard production of essential medicines in Africa should be sustainable. Some commentators have suggested that sustainability in terms of competitiveness can only be achieved with large scale plants that are able to 'achieve economies of scale'. However, the economics of production of final formulations are much more complex, with many factors to consider.

As pointed out in Chapter Two, UNIDO has commissioned various pieces of research into the economics of production for final formulations. They indicate that, with appropriate support and changes in business practices, local manufacturing of high quality products can be competitive with Asian companies.

Long term sustainability of high quality production is possible on the continent and will be a function both of how well companies are run and of progress on a number of fronts (such as harmonization of registration which is being pursued by AMRH). The human resource development solutions outlined in this Business Plan provide assistance to companies on how to run plants efficiently and achieve competitiveness. However, time limited incentives are required to assist companies to make the necessary investments and to protect and support those that have already done so.

The work being done on the economics of pharmaceutical production, coupled with insights as to the current status of production, the investment requirements for upgrades and

the nature of the pharmaceutical industry provide the basis for advising governments on appropriate time limited incentives. These will support the industry as it learns to be competitive and strives to produce to international standards. The recommendations on a package of incentives will be dependent on the specific country context since numerous variables will need to be taken into account, including:

- Interest rates
- Liquidity of equity markets
- Currency volatility
- Current status of the industry in terms of investment requirements
- General and industry specific industrial policy tools and incentives that are already in place (e.g. Special Economic Zones, export incentives, restricted lists, soft loans, etc.)
- The specifics of the tax regime
- Current production capacity and standards in the country
- The specifics of the GMP road map as determined by the NMRA (with advice from the PMPA)
- Public health priorities

These and other variables will inform the design of the package of incentives. Experience from within Africa, as well as other geographies and industries, provides examples of mechanisms that can be utilized to provide fiscal support to manufacturers. They can be largely divided into two categories: direct support and protective measures. Mechanisms for provision of direct support could include:

- Interest subsidies
- Working capital credits
- Underwriting Letters of Credit to improve the credit terms that companies can obtain from suppliers
- Zero rating/exemption for taxes/ tariffs on imported inputs for the industry
- Special depreciation provisions (e.g. in India, companies could allow for 150% depreciation of capital investments)
- Utility subsidies
- Subsidies to support training
- Export incentives

Protectionist approaches could include:

- Increased tariffs on imported finished products
- Restricted lists
- Marginal preference for procurement of locally produced products

The likelihood is that a combination of different tools should be incorporated in an incentives package and, as mentioned, the specifics will inevitably vary from country to country. In advising on an incentives package, we will be mindful of certain considerations. These include:

- Depending on the status of the industry, protectionist policies could be detrimental to public health, for example, if they lead to price increases (e.g. through increased tariffs) or if the local industry is not developed to the point where competition keeps prices down if a restricted list is introduced
- The incentives package will need to recognize the different business models and capital structures that exist and that are desirable for long term sustainability (for example, interest subsidies alone would favour debt financed operations when a blend of debt and equity may be more appropriate)
- The incentives should keep in mind the medium term goal of stand-alone competitiveness and should seek to encourage efficient production (India had price controls in place so that companies had to be competitive from the start but received support in other forms)
- The incentives are intended to be time limited in duration
- Manufacturers are all starting from different points and those that have already made investments should not be penalized. They should receive some form of protection in the short term
- Any measures should be developed to work within the framework of existing industrial policy incentives and mechanisms
- The incentive package should not be overly complicated but should recognize the complexity of the situation
- Measures should be coordinated with the GMP road map (and vice versa)
- The incentives will need to consider foreign investment and joint ventures as mechanisms for sourcing investment and accessing technology as well as the degree to which they should be encouraged through the package
- The incentives should not be token gestures and (based on the evidence) should represent meaningful and appropriate support levels
- The incentives should not represent an unnecessary subsidy to the private sector
- It will be necessary to reflect on the possible “unforeseen” consequences and perverse incentives that could result
- Finally, it should be recognized that incentives cannot resolve all things for all people.

The importance of business skills, energy, initiative, appetite for risk, and ability to adjust of entrepreneurs and corporate managers should not be underestimated, undermined or devalued. Further, these attributes need to be enhanced (as described above) in order to achieve long term sustainable manufacturing across our continent

3.1.4 Insights and guidance on legislative and policy considerations

Policy incoherence has been identified as a major impediment to the development of the pharmaceutical sector. Later in this chapter, we present a proposed approach for developing country specific plans for the sector. The consultative approach across stakeholders and diagnosis of the policy and legislative landscape, followed by development of a shared strategy, are the means by which incoherence can be identified and resolved.

3.1.5 Technical assistance to regulators

Chapter Two identified the critical role of the regulator in the pharmaceutical manufacturing system and pointed to evidence from a recent WHO study that shows that many of our NMRAs (or equivalents) are not able to carry out the necessary functions. The human resource development section of this Business Plan identifies means by which human capacity can be developed and more skills brought into the frame. However, as well as human capital requirements, NMRAs require the infrastructure to fulfil their mandate to protect the public and ensure that medicines on the market are quality assured, safe and efficacious.

Therefore, partners within the consortium will offer technical assistance to produce organizational development plans, including the necessary regulatory infrastructure, and to guide their implementation. This assistance will be provided to both producing and non-producing countries (within the context of ongoing AMRH activities) in order that all nation states have the opportunity to benefit from local sources of high quality production of affordable essential medicines.

The specific functionalities on which the regulator in each country should focus will be dependent on manufacturing aspirations, level of cooperation with other NMRAs, and critical weaknesses in current systems directly relating to protection of public health. There is substantial expertise within WHO and USP that can be brought to bear and the University of Ghana Medical School (designated a WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance (CCATP) in 2010) has developed expertise and a pharmaco-vigilance ‘tool kit’ which could be utilized by the PMPA. However, technical assistance can only deliver progress in this area if there is high level political commitment to invest in the regulatory authorities.

Accessing funding for such institutional development programmes will be the responsibility of member states. However, development banks such as the World Bank have informally indicated that there would be strong interest in requests from governments for loans, soft loans and grants (depending on country status and other priorities) for investment in this critical public health function.

3.1.6 Assistance to leading companies

The long term sustainability of treatment programmes for the pandemic diseases will benefit from establishing high quality WHO certified production. There are three companies in SSA outside South Africa that have reached this standard and a number of others who are working hard towards this (and other stringent regulatory certification).

Fundamentally, this Business Plan adopts a philosophy whereby the whole sector should be supported and required to improve GMP standards and advocates achieving this through building capacity across the manufacturing system. However, there is a public health necessity to rapidly increase local production of international standard drugs for the pandemic diseases. Consequently, the Plan includes support to those leading companies that have already taken bold steps towards achieving international GMP standards. Therefore, some plant level support (based on application to and approval from the PMPA) will be appropriate to assist those that are close to prequalification to reach the requisite standard for products included on the WHO prequalification list. Support will also be offered to those who already have prequalified products so that they can increase their portfolio and access new markets. Achieving WHO approval alone does not guarantee that products will be procured so, in addition to assistance on issues such as dossier preparation, these companies would warrant bespoke plant level assistance to improve their production efficiencies. This would enable them in the short term to be competitive with imports.

Other aspects of the solutions package also provide opportunities for leading companies that have attained WHO standards, including access to new formulations developed under the PMPA and the business linkages platform, under which advanced companies are more likely to be interesting partners for leading international players.

3.1.7 New formulations

Initial discussions have been held with African (e.g. KEMRI and MUHAS) as well as international (Purdue and Howard) universities and centres of excellence regarding their interest in developing formulations for dissemination through the PMPA to companies that achieve WHO GMP standards. Initial interest has been expressed and a model by which such work will be funded and the priorities for formulation development established is under development. It is suggested that the PMPA could provide seed funding for the development of initial formulations and that these would be disseminated to leading companies using a cost recovery model.

This component of the solutions package serves to address some critical weaknesses in the short to medium term, including:

- Expanding the product portfolios of leading companies on the continent to include more than just basic formulations of old products. This will be an important public health contribution
- Developing formulations and then spreading the cost across a range of companies (through charging a fee to each reflecting only a proportion of the real cost) would be a means by which companies could afford to expand their portfolios
- New formulations for Africa are required in some critical areas. Ongoing work by various Product Development Partnerships is looking to address this but the ANDI centres of excellence could coordinate with these other entities to develop, for example, paediatric ACT formulations and novel FDCs for adults and children in the realm of HIV
- Second and third line HIV therapy is largely still under patent protection and prohibitively expensive for many programmes and countries. If TRIPS flexibilities are properly incorporated in our legislation, then we could utilize these centres of excel-

lence to reverse engineer these products and make the technology available to leading African manufacturers. They would then be able to provide such products to the Least Developed Countries on our continent

There is thus a need to assist industry to access products and full common technical document (CTD) format dossiers and to make these high quality dossiers affordable to industry through a 'shared cost' model. The AUC does not intend to provide this service indefinitely. It regards this as an urgent and time limited intervention that will taper off within five to ten years as companies acquire the capability and the financial resources needed to develop their own products.

It is critical to highlight that access to developed technology will be confined to companies who have attained international GMP and will be used as a motivation for companies to work towards international GMP certification. The following key activities will be involved:

- Selecting products for development based on essential medicines lists and second line antiretroviral medicines
- Signing product and technology development agreements
- Reverse engineering products and working with partners to compile CTD format dossiers
- Setting up technology transfer teams and recruiting experts
- Transferring technology to GMP compliant companies

To facilitate commercialisation of the technologies developed by the technology transfer centres, licensing agreements will be directly negotiated with various IPR holders for the issue of voluntary licences for international GMP compliant African manufacturers. Further, given that technology transfer is not a straightforward matter, it is proposed that, on completion of the process and formulation development in various laboratories, the process should then be transferred to Muhimbili University's PharmD R & D Lab, whose laboratory-scale production capacity is up to 5 kg. After this, the process would then be transferred to the Saint Luke Foundation which has a pilot plant with a production scale of 50kg – sufficient to allow bridging from laboratory production to commercial scale. Where such technology transfer is conducted, it will be necessary for a tech transfer team to be established to ensure that the highly involved and complex process is conducted correctly and that recipient companies receive the appropriate training of production staff.

3.1.8 Partnership and Business Linkages Platform

Chapter Two describes the underutilized opportunities for business relationships and various types of collaboration that could strengthen local production. There are a myriad of different relationships that could be entered into and the Business Plan suggests a platform via which these can be brokered. The opportunities for cooperation exist at country and regional levels as well as for intercontinental arrangements to be established to the mutual benefit of both/all parties. Country level collaboration between manufacturers can perhaps best be facilitated through the strengthening of trade associations. Other regional and international linkages could be facilitated through a Partnership and Business Linkages Platform.

There is evidence as to the mutual benefit that various types of relationship could deliver and of the need for our companies to access various inputs, including know-how, capital, products and technology. Despite the evident need and the latent interest in this, the number of relationships that have materialized is limited and the degree to which companies can access investment (through equity joint ventures, professional investors, or bank debt) and know-how (through collaboration or on a fee for service basis) has been reported as a key challenge.

We recommend that an experienced life sciences investment and business development professional be recruited with a dedicated role to manage the various activities that would constitute the Partnership and Business Linkages Platform. The Platform would use various modalities to facilitate partnerships and business arrangements covering the diverse range of potential structures and participants. They include:

- A web portal to include corporate profiles, details of a pool of experts identified for various forms of assistance that companies might require, dissemination of information about upcoming industry conferences, and publication of materials for in-house corporate development programmes.
- Active monitoring and engagement in the flow of business deals in the pharmaceutical sector. This could be achieved through attending conferences and building an extensive network across geographies and types of institution (e.g. research entities, manufacturers, service providers, equipment manufacturers, etc.) with the intention of identifying opportunities for collaboration and promoting opportunities arising out of pharmaceutical manufacturing in Africa.
- In coordination with consortium partners, monitoring the progress made by the sector in mobilizing investment and accessing technology, and identifying opportunities for evolution to the action plan.
- Working with international funding entities such as the Investment Fund for Health in Africa (IFHA), the IFC's Health for Africa Fund and the African Development Bank to mobilize enthusiasm for the sector and to encourage adjustments in investment requirements such as the IFC's prerequisite for WHO prequalification before investing in African manufacturers.
- Holding two matchmaking events over the five year period to provide opportunities for stakeholders to meet and establish initial interest in working together
- Working with strategy development and implementation processes at country level to identify opportunities and recommend approaches designed to facilitate collaboration and to diagnose the investment climate and recommend strategy components that could improve access to investment (e.g. specific aspects of the incentives package that investors would need to see in place)

3.1.9 Strengthening industry trade associations

Most in-country interventions and information dissemination workshops and training sessions will be organized and delivered through large group settings. The AUC and partners will prioritise the strengthening of trade associations both at a regional and country level since they will be valuable partners in the organization of such training programmes and as information dissemination portals.

UNIDO has significant experience in supporting the formation and development of trade associations both in the pharmaceutical sphere and in the wider industrial context. For example, it supported the foundation of the Southern African Generic Medicines Association (SAGMA) and has worked closely with the West African Pharmaceutical Manufacturers Association (WAPMA), the Pharmaceutical Manufacturers' Association of Ghana (PMAG) and the Federation of Kenyan Pharmaceutical Manufacturers (FKPM). Knowledge gained through this experience, together with its institutional strengthening skills, will be brought to bear in assisting the strengthening of industry associations under the auspices of the PMPA.

Trade associations can provide valuable services to their members and can act as a mouthpiece for the industry to raise awareness of the challenges that exist or areas where intervention by government is needed. The associations are also an important means for dissemination of best practice. However, it should be recognized that associations are de facto a collaboration of competitors (creating some internal tensions) and that their job is to represent the interests of their members. It will therefore be important that, whilst the PMPA should seek to assist such associations to develop capacity, their fundamental mandate means that, even when strengthened, they will remain independent from the PMPA core partners. The PMPA is not a mechanism for promoting the wishes of the private sector but it can perform an honest broker function between parties across public and private sectors.

3.1.10 Indirect impact of the PMPA solutions package and opportunities for collaboration

As repeatedly emphasized in this Business Plan, the pharmaceutical manufacturing system is complex and interventions at a number of key points are recommended. However, this Plan cannot and should not attempt to resolve every aspect of the system directly. As described, access to capital and strong related and supporting industries are also imperative to both the short term development of the sector and its long term sustainability.

Certain specific initiatives have been articulated to address these particular aspects. For example, the provision of time limited support, which may include interest subsidies, is intended to enhance access to capital. Similarly, support to artisans and other relevant actors is proposed under the training programme. However, these catalytic initiatives need to be just that - catalytic - with the intention of the plan being to provide the opportunity for governments to address the key dimensions of the manufacturing system and, in doing so, to create new enthusiasm for the sector from associated actors. For example, investors have expressed caution about the sector for a variety of reasons that credible commitment from government in this area (for example, regulatory oversight) would help to address. Those involved in supportive industries may also see new opportunities for establishing capacity on our continent (e.g. in Tunisia, it is viable for international equipment suppliers to maintain offices for servicing their manufacturing equipment given the density of pharmaceutical manufacturers and the advanced nature of the machinery that is used across the board).

Other areas where the PMPA does not look for direct intervention are where there are ongoing initiatives that will provide valuable opportunities for the manufacturing systems on the continent. For example, ANDI has a network of 32 centres of excellence (and is establishing more), some of which already have the competencies and requisite skills to become fully fledged bioequivalence study centres. Through the business linkages activities, and as new formulations are developed under the PMPA, these centres will be engaged for carrying out the clinical component of product development activities. The centres will also be able to assist regulatory authorities with market surveillance activities where these are weak.

The need for less fragmented markets to enable manufacturers to achieve efficiencies of production is a vital long term requirement for sustainable local production. The AMRH work being conducted under the overall framework of the PMPA will be supported, where necessary, under the activities described in this Business Plan. However, the registration and regulatory harmonization components are the mandate of the established parties in this initiative and whilst (as requested) the activities described in this Business Plan can help capacity building at individual regulatory authorities, the Plan defers to AMRH and its partners in the realm of regional integration.

Another area where increased enthusiasm for the sector should provide a virtuous effect is market data. This Business Plan will endeavour to explore means by which data can be collected and disseminated. However, this is an area where substantial expertise is required and, in the developed world, the function is generally conducted by private sector service providers. The implementation of the PMPA and the growing interest in our markets from overseas players may well create a market opportunity for information providers. In view of this, the PMPA will explore interest amongst the likes of IMS Health (through the IMS Institute) as to whether a viable business case can be made for building a platform for data collection and dissemination.

3.1.1.1 Country level implementation

The previous sections have described the generic solutions to be developed under the PMPA. The specifics of how these are implemented at country level will vary depending on the individual country context and its ambitions and aspirations. Therefore, as well as providing a repository of expertise, the Business Plan proposes a process that can assist country level stakeholders to establish their nation's ambitions for pharmaceutical manufacturing and to develop a bespoke strategy and implementation plan for realizing them. Further, once an implementation plan has been developed, the PMPA will (as required) escort the actual execution of the different components of the Plan through accessing the requisite expertise and coordinating the implementation in collaboration with national level stakeholders. Developing national level strategies requires processes to be adopted so that the complex array of considerations and perspectives can be incorporated. Whilst the specifics will vary, an indicative approach that could be adopted at the country level is described here.

In Chapter Two, a schematic representation shows the complexity of the pharmaceutical manufacturing 'system' and identifies the roles of the many types of stakeholders involved. Historically, it has been suggested that there are mutually exclusive, non-compatible, perspectives amongst this diverse range of actors. However, experience suggests that, through a consultative process and a thorough diagnosis of the specific objectives, mandates and challenges faced by individual actors, it is possible to develop a comprehensive strategy that

can be endorsed by all parties. Experience also suggests that high level political engagement from the outset is critical if rapid progress is to be made from the time of initial engagement between parties through to strategy development and implementation.

The nature of the process for designing and implementing a strategy at national level is therefore a critical part of the 'package' of solutions. As with all other areas of the PMPA, the specifics will depend on the context. However, an indicative approach is described below.

Stage 1: Project set up

On receipt of an invitation from the government of a country, PMPA representatives will have initial discussions with the key stakeholders to determine an agreed approach for diagnosis, consultation and strategy development. The key stakeholders are likely to include the Ministries of Health, Industry, and Finance (or their equivalents), the NMRAs, academia, and industry representatives. The discussions would likely include the establishment of a working group with high level representation from the key stakeholders. This group would provide oversight for the development of the strategy and its implementation and would also establish the activities to be conducted and milestones to be set and draw up a timeline for their completion.

The stages now outlined would be dependent on these initial discussions, so, once again, they should be seen as indicative rather than cast in stone.

Stage 2: Situational analysis

A situational analysis will involve collection of hard data on, for example:

- Health budgets
- Pharmaceutical expenditure
- Current industrial policy frameworks and industry development support, as well as other pertinent policies and legislation such as IPR and national procurement rules
- Taxes and tariffs applicable to the industry
- Imports and exports
- Range of products produced
- Access to capital considerations (such as interest rates, currency volatility, equity markets)

It will also include a qualitative component in which the different stakeholders (including entities such as civil society and the donor community) are engaged to garner their perspectives on the pharmaceutical sector, including the major challenges faced.

Consequently, the situational analysis will capture key hard data but, more importantly, will be a consultative process whereby the different perspectives and the consequent implications and concerns about strategic direction are captured at the outset.

In collaboration with the working group, PMPA representatives would produce a report on the findings to be submitted to key stakeholders for consideration prior to a 'round table' where stakeholders would discuss the findings and initial proposals on ways forward.

Stage 3: Detailed strategy design

Subject to the conclusions of the round table, the expertise outlined in the PMPA 'solutions package' would be mobilized to work with specific stakeholders to tailor a package of interventions based on the strategic vision articulated by the round table. The detailed work (such as developing a package of incentives or determining the needs of the regulator regarding its capacity) will need to be conducted separately. However, a key function of the PMPA representative will be to ensure that the specific deliberations are put together in a manner that ensures that they are mutually reinforcing and represent a coherent holistic approach to developing the sector.

For example, detailed work on industry incentives that may need to take place with the Ministries of Finance and Industry should be coordinated with the detailed work with the regulator and industry on establishing a GMP road map. The incentives (and other aspects of the strategy) will need to be aligned with the requirements of the road map. This is the case both from a timing perspective and in terms of reinforcing the regulatory requirements whereby incentives may be triggered upon achieving certain milestones. Unless this is done, progress at the implementation stage is likely to be highly problematic.

Where there is an established industry, subject to approval by the regulator and other government bodies, a diagnostic (as opposed to regulatory) GMP audit should be considered at this stage. This will provide a baseline for purposes of monitoring and evaluation and a basis of understanding for developing an upgrading schedule and programme for the country. A generic GMP road map will be developed as a central solution but, unless it is tailored according to the specific country reality, its value may be compromised. Similarly, the risk assessment of the EML will be a guide and local considerations will need to be reflected in any specific limitations adopted on manufacture.

This detailed strategy design phase will produce an overarching articulation of the strategy and an implementation plan. This plan will, where appropriate, involve specific organizational development plans for the regulator and the industry association. It will also identify any policy or legislative requirements that need putting in place. The strategy will involve a detailed cost benefit analysis for consideration by government, whose authority at the highest level would be required to move to implementation. Following consultation with government, it will also include indicators by which progress towards the vision can be assessed.

Stage 4: Implementation

The pharmaceutical industry is complex, capital intensive, and, at the plant level, calls for detailed expertise and sophisticated processes, equipment and facilities. If these are not already in place, they will take time to develop. Similarly, the capacity of the National Medicines Regulatory Authority is critical to the development of the industry. However, putting in place the appropriate regulatory systems is likely to require enhanced human resources and organisational development, neither of which can take place overnight. Consequently,

the implementation phase of the work will need to recognize that momentum and political will must be maintained over a period of years.

It is expected that, through coordination under the PMPA, the partners will be able to move from talk to demonstrable action at the country level and that this will be an important component in maintaining momentum. Appropriate government structures should also be established and specific aspects of the national pharmaceutical industry development plan should be incorporated into the performance metrics for organizations and individuals.

In Chapter Four, a proposed structure for implementation of the Business Plan is outlined. It recommends that regional PMPA coordinators should oversee activities in individual countries that would be managed on a day to day basis by national experts. It would be the role of these regional coordinators to access the expertise of the consortium and the generic solutions package in order to ensure that national level implementation plans are conducted as approved by the governments of each country. The representatives of the PMPA based at regional and country levels would also, where invited by the Government, be responsible for ensuring that developments are coordinated. In addition, they will be empowered to identify specific challenges present in any particular country and to mobilize expertise under the PMPA to address them.

The specific activities carried out under the implementation phase will take place over a period of years and will represent combinations of generic solutions described earlier and tailored to the country context as well as bespoke solutions where necessary.

This central package of solutions is intended to provide the flexibility to advise and assist countries facing very different contexts. Whilst the complete range of activities may be required in some hubs that aspire to enhance manufacturing, other aspects may not be relevant in all contexts. For example, the GMP road map component will have no relevance to a country such as Botswana, which is looking to establish pharmaceutical manufacturing capacity from scratch and therefore does not require a quality upgrading road map. Similarly, the availability of a central repository of expertise will enable the PMPA to assist other non-producing countries or those with very small pharmaceutical sectors to consider their options. For example, technical insights and understanding of the business and public health aspects of local production could be mobilized to support countries such as Chad and others to determine whether they wish to develop a strategic asset in this space and to develop the model (perhaps a Public Private Partnership - PPP) by which one could be achieved.

3.2 OTHER ACTIVITIES

In addition to the generic solutions package, there are other initiatives proposed by this Business Plan including the need for certain activities at the sub-regional and continent level, as well as further work on developing strategies for parts of the Essential Medicines List and production value chain not already covered by the central solutions.

The manufacturing of formulations is part of a value chain which extends back to the production of raw materials including APIs. The core of this Business Plan looks at enhancing the formulations component of the value chain on the continent. However, long term sustainability, competitiveness and innovation aspirations need to take into account enhanced

API capabilities at the continent level. In the shorter term, there are also likely to be opportunities for local production of other inputs.

This Business Plan covers various formulation types but focuses largely on small molecule products. There are other products on the Essential Medicines List for which local production is very desirable, particularly blood products.

3.2.1 Initiatives at continent level

There is a growing interest in local production of generic pharmaceuticals amongst our development partners, an evolution in approach that is to be welcomed. We established the concept of the PMPA as early as 2005 and the plan itself was endorsed in 2007. As emphasized earlier, the PMPA respects the sovereignty of individual nations to take decisions and to work bilaterally with institutions as desired. Similarly, the autonomy of our Regional Economic Communities is also respected by this Business Plan and interventions at both levels under the PMPA would be subject to invitation from the respective political bodies.

However, the AUC will provide a central hub where those interested in continent level plans which impact on the pharmaceutical industry will be able/expected to discuss their plans and to align behind the PMPA. For example, the AUC, working with a consortium of partners able to provide expertise and insights on many fronts, would have been an appropriate partner in advising on the design of the AMFm, which has implications for the sustainability of our local industry. The malaria community is to be congratulated that it recognized this issue and took steps to address the concerns of local industry and seek solutions through its conference in Nairobi.

In future, those working on public health initiatives and policy changes at, for example, the Global Fund, will be able to seek input from the AUC (with advice from the consortium) when they consider the impact of initiatives on the long term sustainability of local production. For example, the Global Fund's market dynamics committee may wish to confer with the AUC and its partners as it considers procurement policies that could assist in increasing access to essential medicines and looks to transition to a future model where we will take an increasingly large share of the responsibility for providing essential medicines for our people.

The TRIPS flexibilities issue is another area where a continent wide position and the ability to speak with one voice will have increased weight in discussions on extending the flexibilities. Working together with international organisations like ARIPO, UNDP and UNCTAD, the PMPA partnership will join the effort to lobby for the extension of the January 2016 TRIPS flexibilities window. The partnership will also mobilize all those involved to lobby for the simplification of requirements to exploit the flexibilities given that the current onerous and time consuming process has seen many companies either abort or elect not to participate, even when an opportunity presents itself.

3.2.2 Regional level initiatives

There are a number of legislative, policy and trade issues that need resolving at the regional level. They include the regional framework for incorporating TRIPS flexibilities, registration harmonization, and strategy frameworks under which national level progress can be made. Equally important is the need for cooperation to maximise the benefits of pharmaceutical trade among our countries and to minimise the impact of protectionist policies among partner states that could stand in the way of mutual benefit and progress. In view of this,

the consortium of partners would be available to assist regions to resolve some of these issues, subject to invitation, and could forge links between national level strategies and the frameworks put in place at regional level. Moreover, where regional level strategies are as yet incomplete, the AUC and its partners could also work with the regional departments of health, industry and trade to assist various counterparts to work together to establish policy coherence at the regional level.

3.2.3 Regulatory harmonization

Lack of regulatory harmonization presents a serious challenge to manufacturers and inadvertently leads to reduced access and higher prices due to reduced competition when some companies opt out of certain markets. Resolving this conundrum is thus critically important. There are a number of very good ongoing initiatives under the auspices of the AMRH initiative led by NEPAD among others.

The AMRH initiative has been working in the area of medicines regulatory harmonization since 2006 and has to date developed a number of regional proposals for harmonization in a number of RECs. The harmonization processes for RECs like the Southern African Development Community (SADC), Economic Community of Central African States (ECCAS) and Economic Community of West African States (ECOWAS) are at an advanced stage and the East African Community (EAC)'s plan has been finalized and was formally launched in March 2012. Lastly, the AMRH has also been mobilizing political support and the financial and technical resources needed to bring this to fruition.

Given that the lack of capacity in some NMRAs is partly responsible for the low levels of trust among respective Authorities, the training of regulators is a key intervention on which the partnership will focus. The remaining harmonization initiatives will continue to be ably managed by the AMRH and it is envisaged that the role of this Business Plan will be confined to supporting the development of country policies and strategies conducive to regulatory harmonization and to offering support to the activities of the AMRH through ongoing technical assistance and training and capacity building of NMRA employees.

3.2.4 Taking advantage of TRIPS flexibilities

One of the key policy and legislative changes needed in order to benefit our continent, its patients and local industry is in the domain of intellectual property rights. Most countries have failed to take advantage of current opportunities presented by TRIPS flexibilities. A few have enacted the TRIPS provisions but the common consensus is that the requirements are too onerous and too time consuming. Exploitation of the provisions is only permissible if they are written into national laws yet many LDCs have not even incorporated TRIPS flexibilities into their national legislation for the reasons cited above. In fact, not only have LDCs not incorporated the flexibilities, some actually have far stricter IPR than required under the TRIPS agreement.

Furthermore, negotiations to extend the window period beyond January 2016 should be intensified and Africa should push for another ten year transition period. The AUC firmly believes that the TRIPS flexibilities present the same opportunity for African pharma as did the Indian Patent Act of 1970 for Indian industry. The Commission is convinced that full exploitation of the flexibilities would lead to a transformation of local industry. Therefore, working together with ARIPO, UNDP and UNCTAD, the PMPA will:

- Lobby for simplification of the means by which flexibilities can be exploited. The current system is onerous and wasteful
- Advise and assist governments to revise and amend their patent laws to incorporate the flexibilities
- Assist international GMP compliant Africa based companies wishing to make full use of the flexibilities in order to supply LDC markets with the documentation and in negotiating the legal minefield
- Work with RECs to harmonize national patent laws to facilitate exploitation of the flexibilities for the benefit of the continent

This initiative creates an avenue to partner with European and North American companies who often develop molecules considerably ahead of time. Some of these companies have already developed molecules whose patents will expire in 2017 and beyond. Given that they have already committed the funds and invested in product development, they could transfer the technology to international GMP compliant African manufacturers who can then exploit the TRIPS flexibilities and market these much needed drugs in LDC markets.

3.2.5 API production

Measures to enhance API production capability on the continent are worthy of detailed consideration in view of their potential to impact on the sustainability of production and to become an asset for innovation (e.g. through novel synthetic pathways). The level of API production on the continent at the moment is minimal but due consideration will be given to enhancing capabilities and the models by which this could be achieved (such as the PPP approach with Lonza in RSA) as a discrete part of the PMPA.

Whilst the production of various APIs remains a long term ambition, in order to exploit the TRIPS flexibilities, our continent will need to develop the competencies to manufacture its own APIs for products like second line ARVs. This is necessary given that the large Asian bulk drug producers would, in the absence of voluntary licences, be unable to manufacture and supply API to local formulators. Similarly, the owners of the intellectual property would be unlikely to provide API to our manufacturers even though our market contributes only a minuscule amount to their revenues for any given products. Our partnership with leading academics who have the expertise and have already developed a number of environmentally friendly, more efficient and less costly processes for developing various molecules will be very valuable.

3.2.6 Blood products

The collection of blood, and the separation of different components into plasma, various blood factors, platelets and red blood cells is a specialized process that has limited correlation to the generic pharmaceutical production which is the focus of this Business Plan. However, the availability of blood products in Africa would benefit greatly from local capacity for collection, fractionation, etc. WHO is proposing to conduct feasibility studies on the expansion of blood product production on the continent. This work is welcomed by the AUC and, once initial findings are developed, could be incorporated as a component of the PMPA.

3.2.7 Vaccines and biological products

An area that will require further work is establishing a model for enhancing the production of human vaccines. Vaccines are a cornerstone of any primary healthcare programme and are an essential tool in preventing disease. The significance of vaccines in public health in general, coupled with the requirement to be able to respond rapidly to pandemics (note the limited availability of flu vaccines during the 2009 influenza crisis) mean that developing our own capability to provide for our vaccine needs will be explored. The African Vaccine Manufacturers' Initiative is currently being formulated. Historically, much emphasis has been placed by international agencies and donors on the supply of vaccines and in doing so many lives have been saved. However, we should build production capacity on the continent so that, in the medium to long term, we will be able to rapidly respond to our needs and will have a sustainable source of high quality products to address vaccine preventable diseases.

Developing our continent's ability to produce biological products also needs further consideration. A number of important medicines based on recombinant DNA technology were developed with the advent of biotechnology in the latter part of the 20th century and the field continues to be a source of novel treatments. In the realm of diabetes, recombinant human insulin and epithelial growth factor are critical for managing the disease and associated symptoms; biological products have improved efficacy for many diseases compared to some earlier generation treatments (e.g. tumor necrosis factor inhibitors for the treatment of rheumatoid arthritis and betainterferons for treating multiple sclerosis); and a number of the of latest generation cancer treatments are biological products (e.g. trastuzumab – trade name Herceptin – a monoclonal antibody for the treatment of breast cancer). As 'Western' and non-communicable diseases become more prevalent having affordable, quality assured sources of such products and others will be vital for providing our people with the best treatment options for some emerging public health issues. We currently have very limited capacity for production of biological products and will need to consider different models for the development of this segment of the industry given the unique manufacturing, distribution and market considerations that apply. Biotechnology may also hold the key to treating uniquely African diseases and provide an option for optimizing traditional medicines, thus building R&D expertise in this field as well as production capacity should be part of the objective.

3.2.8 Traditional medicines

Our continent is home to a large and diverse plant life, much of which has formed the basis for many of our traditional medicine systems. It is also a fact that these plant based remedies remain the treatment of choice for many people in Africa. The AUC is acutely aware of this and, of course, the PMPA itself recognizes the important role that traditional medicines play in healthcare delivery on our continent. Whilst research has been carried out on some of the most well known treatments, and notwithstanding the fact that some have even been commercialized by international companies, there is an urgent need to accelerate research into the extensive flora, especially those for which medicinal claims are made.

This process would lead to the codification of the traditional medicines and an elucidation of properties, side effects and related aspects of the plant life, as well as the creation of a library for these findings. The AUC is very aware of the potential value of such medicines and believes that the diverse African flora may well provide the world with another wonder drug to replicate the importance of artemisinin, which has been used in traditional Chinese medicine for centuries. The USP is proposing to establish a Medicines Compendium for drugs

used outside the US and this would include traditional medicines. Moreover, initial discussions have taken place with experts in the field about approaches that could be adopted to enhance availability and consistency of effective traditional African remedies.

3.3 SUMMARY OF CHAPTER 3

The key messages from this Chapter include:

- The heterogeneity of contexts across our continent requires that a solutions package is designed to be flexible and able to assist countries at various stages of development in the pharmaceutical field and with differing ambitions
- The various dimensions of the pharmaceutical manufacturing system and the ‘inter-connectedness of issues’ mean that implementation of different ‘solution modules’ in a country must be coordinated as part of a holistic strategy for development of the sector
- The Business Plan proposes a Generic Solutions Package across dimensions that include approaches for strengthening human resources, guidance on incentives to the industry, the utilization of a GMP road map and associated risk assessment of the EML, brokering of partnerships and business linkages, and assistance to strengthen regulatory capacity
- A process for developing and implementing national level strategies upon invitation from governments would likely include initial discussions with key stakeholders, a detailed consultative and diagnostic process, detailed strategy design, and implementation
- This process and the solution packages could be implemented in all countries ranging from those with no ambition to enter into manufacturing but with a desire to improve regulatory oversight and to benefit from high quality local production from neighbours to advanced countries in the North who wish to further develop their industries for public health and economic development objectives
- This Business Plan espouses an approach whereby the industry as a whole is assisted and required to improve standards to eventually achieve international GMP. However, in the short term, individual assistance to leading companies to prequalify products is also a critical requirement
- There is the need for novel formulations such as new FDC ARVs and paediatric ACTs. The opportunity also exists to take advantage of TRIPS flexibilities through reverse engineering of second and third line ARVs. In view of this, research centres will be assisted to develop such products for transfer to companies that meet international GMP standards
- Implementation of solutions and genuine commitment from partners and governments will lead to indirect improvements in the business context for the pharmaceutical industry by, for example, making it more attractive to investors and through the establishment of supporting services and industries

- As well as country level activities, this Business Plan identifies some additional areas of work at regional and continent level (such as lobbying for an extension to the TRIPS flexibilities) and identifies associated areas such as API production, blood products and traditional medicines where ongoing work will need to be built upon and insights incorporated under the PMPA

4. IMPLEMENTATION PLAN

The earlier Chapters of this Business Plan have detailed the ambitions for pharmaceutical manufacturing on our continent, outlined the current situation in the sector and the challenges and opportunities in realizing the vision of the PMPA. They have also proposed an indicative ‘package of solutions’ that will be developed to address the complexity of the various dimensions of the pharmaceutical manufacturing system in a holistic and coordinated fashion. This package of solutions will represent a central repository of expertise that can be tailored to implementation at the country level.

The main thrust of the document is that, whilst ambitions and aspirations vary amongst our member states, there are generic themes that apply to a greater or lesser extent across countries that are actively engaged in pharmaceutical production or in those that may wish to enter the sector. Critical to the design of this proposal for implementation is that the solutions required cover a diverse range of skills, expertise and capabilities which no one organisation or entity can provide. In view of this, a consortium approach, with core partners contributing to the design and implementation of the solutions package, is recommended. Initial discussions have taken place with organisations identified as having the critical expertise and mandates to cover the range of requirements. During the initial stages of implementation, detailed discussions will be necessary to lay the foundations of the consortium and to establish the specific roles and responsibilities of the different parties.

If this Business Plan is to translate into genuine sustainable progress to the benefit of our continent, it is imperative that the partners (both African entities and international development bodies) within the consortium genuinely collaborate over an extended period of time and that a positive dynamic is established between the various organisations. The achievement of a functioning consortium will be dependent on a number of factors, including:

- The degree to which partners have the opportunity to provide input into the details of what this Business Plan will deliver and how this will be achieved
- The availability of central resources to fund the activities of various parties under the PMPA
- Establishing mutual trust between organisations and between the individuals who represent them
- Establishing the legal basis for the consortium
- Developing a detailed shared work plan with roles and responsibilities identified along with the measures by which organisations will be held accountable for their contribution
- The governance and reporting structures for the consortium
- The degree of flexibility for the work plan such that learning over time can be incorporated and activities adjusted according to the evolving reality on the ground (subject to oversight from the PMPA governance structures)
- The central authority of the African Union Commission as the leading entity which ‘owns’ the plan on behalf of our member states

This implementation plan is crafted with a clear recognition of the multiplicity of efforts and initiatives across the various RECs and countries on the continent. Whilst it recognizes the need for some regional interventions, it also appreciates the crucial importance and centrality of country level implementation. Key to real progress at the country level will be the coordination of activities on the ground and the collaboration between a diverse range of national level stakeholders. As well as coordination at the central level, this Business Plan proposes a mechanism by which (subject to invitation by individual member states) agents acting on behalf of the PMPA will be able to fulfil an ‘honest broker’ role as national level stakeholders come together to formulate, develop and implement a shared national strategy for the development of the ‘Pharmaceutical Manufacturing System’.

The PMPA is an African initiative and is the responsibility of the AUC on behalf of our member states. We have invited UNIDO to be a core partner in accelerating the implementation of the PMPA and it has agreed to continue in this role as we move to implement this plan. UNIDO will also work with us as we set up the consortium of partners and seek to mobilize the necessary resources.

Moving forward, it will be imperative that the consortium is a partnership under the leadership and authority of the AUC. UNIDO has been asked to provide planning and coordination functions at the central and field level as part of the role it will fulfil in this partnership. The Organization has indicated that, backed by financial support from the German government, it will be self-financed as it works with us through the initial phase of the Business Plan.

In the longer term, central funds (mobilized for the implementation of the PMPA) will be allocated and disbursed according to the shared work plan developed by the partnership on condition that this work plan is endorsed by the governance structures of the PMPA/AUC and the respective donors.

A phased approach to the implementation of the Business Plan is envisaged. This chapter first describes the various phases to be worked through. It then details specific components of implementation such as the nature of the resources required, a proposed structure, approaches for engaging the broad range of stakeholders operating in this field, and finally discusses the monitoring and evaluation dimension of the plan.

4.1 PHASED APPROACH TO IMPLEMENTATION

Four main phases for the implementation of the plan are envisaged:

- Set up phase
- Pilot phase
- Scale up phase
- Full scale implementation

The following sub-sections describe in more detail the activities to be conducted during each phase. It should be noted that a strict linearity is not anticipated and, for example,

given that a few countries and regions have already developed plans that are ready for further elaboration, the pilot phase is likely to overlap with the set up phase. Moreover, whilst it has been designated as a specific ‘phase’, perhaps an alternative way of perceiving the pilot phase is that it provides for the launching of full scale implementation in countries that have already developed plans of action and where the solutions developed in the set up phase can be implemented without the need for the consultative process required in most countries.

4.1.1 Set up phase

The set up phase will involve the following key aspects:

- Building the consortium and establishing its legal basis
- Detailed discussions to develop a shared work plan
- Resource mobilization
- Development of solutions for which further work is required (e.g. GMP roadmap, EML risk assessment, detailed design of syllabus for HR development across the different dimensions of human capital requirements)
- Identification of member states and, if appropriate, RECs who wish to actively engage with the PMPA
- Identification of experts and service providers
- Interaction with other stakeholders involved in activities related to pharmaceutical manufacturing in order to derive inputs and identify opportunities for collaboration/alignment with the PMPA
- Setting up field representation for the PMPA

Establishing the central consortium

Initial discussions have taken place with prospective partners in the central consortium that would assist the AUC in the implementation of this Business Plan. This consortium should include partners with sufficient expertise to cover the full range of disciplines required for the pharmaceutical manufacturing system, including regulation of the industry, industrial development, GMP, human resource development, and formulation development/R & D, as well as political authority in the realm of public health. It will comprise African organizations and international development partners but should consist of a limited number such that it does not become unwieldy. Consequently, whilst some overlap in expertise is inevitable, duplication of expertise will be limited.

The introduction to this chapter identified some of the aspects needed for the consortium to become a genuine partnership with positive internal dynamics so that it is able to effect change. One component of this is establishing the legal basis for the consortium and further legal advice will be required as to the specifics of the appropriate legal structures. Partners will also be expected to sign memoranda of association or letters of agreement that identify the fundamental role that each organization will play.

Whilst a legal basis for the relationship between the parties is required, it should also be borne in mind that extended deliberations should be avoided as there is an urgent need for progress on the ground. The legal documents will outline the core role of each constituent but will in all likelihood also refer to the action plan for identification of the detailed activities to be undertaken by each partner. Such an approach will enable flexibility since the action plan should be a 'living document' that will be reviewed regularly with substantive changes submitted to the Technical Committee and respective donors for approval. Furthermore, it should facilitate a relatively efficient approach to establishing the legal basis for the consortium.

Developing a shared action plan

Once agreements in principle have been reached with partners, the development of a shared action plan will be a top priority. Initial bilateral discussions will be held between the AUC/UNIDO and different potential partners prior to a proposed retreat when the consortium will meet to discuss and agree on the details of the shared action plan. This plan should represent a common understanding of the detail required for each component of the solutions package and will probably include indicative (depending on resource mobilization progress) timelines for production of concrete deliverables. The specifics of the action plan will enable a detailed understanding of the magnitude, nature and timing of resource requirements and will feed into the resource mobilization activities conducted by the AUC and UNIDO.

Resource mobilization

A description of the resource requirements for the Business Plan is given later in this chapter. AUC/UNIDO will take the lead in developing and implementing a resource mobilization strategy. This will involve initial contact with donors to explain the philosophy and recommended approach of the Business Plan for the PMPA and to explore their level of interest. This Plan provides indicative figures as to the timing and magnitude of resources required over the next five years and this will form the basis for discussions. However, the action plan will need to be finalized before detailed negotiations can take place and in order to establish the monitoring and evaluation requirements of the funders of this initiative.

Further development of the solutions package

The current status of the individual components of the indicative solutions package varies. For example, deep insights into regulation of the industry are inherent within the expertise of potential partners such as WHO, although the implementation of this Business Plan will require the scaling up of ongoing activities and identification of technical expertise that can be mobilized (probably on a fee for service basis) in order for technical assistance (TA) across different countries to be delivered in parallel. Similarly, UNIDO has extensive experience in working with countries to develop strategies across the manufacturing system and a proposed stepwise approach to engaging with stakeholders is described in this document.

However, other aspects, such as the development of a generic GMP roadmap, need more work. WHO has (in another context) identified the risk assessment of the EML as being a potential activity for the near future and discussions as to how this can be supported by the

PMPA will be necessary. Various academic institutions in Africa have the capability to develop new formulations but the products to be developed will need prioritizing. A comprehensive syllabus for developing human resource capacity across the manufacturing system largely exists across different stakeholders. However, the critical issue is to ensure coordination of the syllabus in such a way that it builds on itself over time. This will require further deliberation during the set up phase.

In view of this, during the set up phase it will be necessary to refine existing tools and expertise as well as to ensure that substantive progress is made on certain specific elements of the solutions package.

Identification of interested member states and RECs

We will invite expressions of interest from our member states to establish which countries and possibly RECs would like to work with the AUC and its partners. The Business Plan is designed to benefit all countries on our continent whether through strengthening the manufacturing system itself or through providing secure sources of high quality affordable medicines across much of the Essential Medicines List. The PMPA is not intended to be a funding mechanism for public or private sector investment but is a proposed package of technical assistance that would be provided to enable countries to fulfil their ambitions in this field and to help develop and implement tailored strategies that take into account the specific context of a country or region.

For countries that do not seek to become manufacturing hubs, the PMPA would look to provide guidance on improvement in regulatory oversight to enable them to take advantage of high quality regional sources of supply. Such activities would be conducted in coordination with other ongoing initiatives (such as the AMRH work and regional strategies) and will not seek to override these endeavours. However, improved market oversight is a key requirement if the benefits of local production are to be realized and the AUC and its partners would seek, where necessary, to increase the emphasis on this aspect and to mobilize the requisite support such as loans from development banks for investing in regulatory infrastructure.

Subject to the number of requests received, as well as available resources and the timing of those resources, it is likely that some means of prioritizing requests will be necessary. Depending on the volume of demand, the AUC would seek guidance from the Technical Committee as to the criteria to be applied when scheduling support for individual countries. Ultimately, the prioritization would only be relevant during the set up, pilot and scale up phases as, at full implementation (subject to available resources), the AUC and its consortium partners would look to work with all countries requesting support to establish their priorities and develop and implement the strategy for achieving them.

Identification of service providers

In addition to the consortium of partners, there will be a need to engage external expertise from service providers in the realm of, for example, improving production efficiencies, advice on accessing the best technologies, and so forth. The AUC will, through the business linkages platform, identify a number of experts who are available to work with trade associations to disseminate best practice and, secondly, to assist companies willing to pay for

additional in-house training which would build on the sector level modules and materials developed for manufacturers to utilize.

Interaction with other stakeholders

Of necessity, the size of the central consortium will be kept to a limited number of organizations. However, many entities are active in areas related to local production and their partnership with the PMPA and alignment with its approach will be critical to the success of this endeavour. Therefore, as well as the establishment of a consortium, mechanisms by which other partners can be engaged for inputs and for coordination will be explored. In the initial set up phase, for example, bilateral discussions between the AUC (and/or UNIDO acting on behalf of the AUC) and the many entities involved would be appropriate. A stakeholders' conference would also be a possible mechanism for building awareness, seeking inputs and allowing for constructive debate as to how different parties could align with the overarching objectives of the PMPA.

It is also likely that, although not members of the central consortium, other stakeholders could become directly involved in implementing activities through direct funding of their activities from central PMPA resources. For example, there are a number of academic organizations in Africa that have expressed interest in working with the PMPA and it is essential that Africa's academia should be represented within the consortium. However, it will not be possible to have all such institutions represented even though they may be conducting critical functions under the PMPA (training, formulation development, etc.).

Setting up field presence for the PMPA

Experience suggests that there is a need for an 'honest broker' function at the country level to bring different stakeholders together to develop shared strategies for the manufacturing system. It has also been established that such collaboration requires close escorting so that momentum is built and maintained. It is therefore proposed that a dedicated (though minimal) field presence be established, with coordinators covering a number of different countries. A proposed structure for implementing the PMPA is elaborated later in this chapter.

4.1.2 Pilot phase

Given that various organizations have already been working in some of the identified priority areas in some countries, the package of PMPA solutions will be mobilized in those territories where there is already broad consensus among stakeholders about what needs to be done. USP, UNIDO and WHO have, for example, all been actively engaged in Ghana and Kenya on various dimensions of the local production agenda. Furthermore, through a stakeholder consultative process, strategies have been developed that are supported by the different national actors across public and private sectors. In view of this, these countries would be well positioned to benefit immediately from implementation of solutions and could therefore be considered for assistance as part of the pilot phase.

It should be highlighted that the pilot phase is not envisaged as reaching a 'conclusion' prior to scaling up of activities as progress in the pharmaceutical sector will materialize over an extended timeframe. However, there will be the opportunity to learn how the consortium

works at the country level and to seek to adjust the model as experience is gained. It is intended that the scale up phase (subject to resources) will take place in parallel with activities in these countries although strategy development at the national level will be needed prior to detailed implementation.

4.1.3 Scale up phase

Ultimately, the PMPA is designed to be a mechanism by which real progress can be made on the ground in our member states. Many countries do not have strategies for the pharmaceutical system. Consequently, prior to delivering change, national (and regional) strategy development exercises will be necessary.

In view of this, the scale up phase refers largely to the need to enter into detailed strategy design at the country level prior to implementation. Subject to demand from our member states, resource mobilization, and the level of capacity available for field level coordination under the PMPA, it is likely that some means of prioritizing countries will be necessary as already pointed out. The Technical Committee's guidance on this matter will be sought. However, it is worth reiterating that such prioritization is purely a scheduling issue and that the development of national level strategies for all interested countries would be initiated as expeditiously as possible.

4.1.4 Full scale implementation

Some countries have already developed strategies that can be built on through a detailed implementation planning process followed by the implementation itself. Therefore, it is proposed that the PMPA move rapidly to conduct this work under what is described as the pilot phase. Full scale implementation will effectively be the phase when strategy design from other interested countries comes on stream and the PMPA is mobilized to deliver the tailored package of solutions in-country.

4.2 STAKEHOLDER ENGAGEMENT

This section identifies the broad range of stakeholders and reviews the steps needed to engage them and align efforts behind the PMPA. It will also outline a plan for maintaining the channels of communication with all stakeholders.

The AUC recognizes that one of the reasons why various pharmaceutical development initiatives have not achieved the desired success is the lack of participation and coordination across various stakeholders. To ensure that there is widespread support and buy-in from all stakeholders and that their activities are consistent with objectives, the AUC will seek to involve all interested parties throughout the various phases outlined in the Business Plan. The Commission has thus undertaken a stakeholder mapping and analysis which takes into consideration the current initiatives in place to support local manufacturing on the continent. It also includes direct beneficiaries such as industry trade associations, individual companies and the patients who will benefit from the realization of the PMPA's goals.

We propose to develop a plan to establish and maintain channels of communication with all stakeholders such that they are kept informed and can provide insights and feedback on

their activities. We at the AUC will also be a focal point with which any organizations whose activities in Africa are relevant to the sustainability of pharmaceutical manufacturing on our continent will be able to/expected to engage. In this way, we will seek to ensure that policy incoherence at the continent level as a result of uncoordinated initiatives does not materialize. The AUC is nonetheless aware of a number of good initiatives on the ground and has no intention of interfering with bilateral initiatives at a country or regional level that have been entered into by our member states or RECs; we will only seek to augment efforts on the ground and not to supplant them.

The African Union Commission will therefore develop a stakeholder engagement strategy which will likely involve communicating information on developments under the PMPA and the establishment of mechanisms by which stakeholders can come together to provide feedback and to discuss their activities under the overarching PMPA framework. Table 4 lists some of the present and potential stakeholders (but is by no means the definitive list) and the areas in which they are active.

Table 4: Indicative list of the broad array of stakeholders in areas related to pharmaceutical manufacturing in Africa

<i>Area of Work</i>	<i>Organization</i>
Human capital development and capacity building (production and business management)	<ul style="list-style-type: none"> • Action Medeor • African academic institutions • African Medicines Regulatory Harmonization initiative (AMRH) • Howard University • International Conference on Harmonisation • Purdue University • Saint Luke Foundation in Tanzania • Stringent Regulatory Authorities (e.g. FDA) • U.S. Pharmacopeial Convention (USP) • World Health Organization (WHO)
Intellectual property	<ul style="list-style-type: none"> • African Regional Intellectual Property Organization (ARIPO) • Deutsche Gesellschaft fuer Internationale Zusammenarbeit (GIZ) • United Nations Conference on Trade and Development (UNCTAD) • United Nations Development Programme (UNDP) • World Intellectual Property Organization (WIPO)
Procurement	<ul style="list-style-type: none"> • Clinton Health Access initiative (CHAI) • Global TB Drug Facility • Medecins Sans Frontieres (MSF) • National Tender Boards • President's Emergency Plan for AIDS Relief (PEPFAR) U.S. • The Global Fund to Fight AIDS, Tuberculosis and Malaria • UNICEF • UNITAID

Area of Work	Organization
Policy and general	<ul style="list-style-type: none"> • GIZ • Southern African Regional Programme on Access to Medicines and Diagnostics (SARPAM) • UK Department for International Development (DFID) • UN Agencies
Funding institutions	<ul style="list-style-type: none"> • African Development Bank (ADB) • Equity investors • Industrial development Corporation (IDC) (RSA) • International Finance Corporation (IFC) • Other Banks
R&D, bioequivalence and centres of excellence	<ul style="list-style-type: none"> • African Universities • African Network for Drugs and Diagnostics Innovation (ANDI) and its Centres of Excellence • Council on Health Research for Development (COHRED) • Drugs for Neglected Diseases Initiative (DNDi) • Howard & Purdue University
Potential partnering organizations	<ul style="list-style-type: none"> • European Generic Medicines Association (EGA) • Indian Drug Manufacturers' Association (IDMA) • Indian Pharmaceutical Association (IPA) • Other international pharma associations
Potential international collaborators	<ul style="list-style-type: none"> • Health Action International (HAI) • Kenya chapter of the Pan African Treatment Access Movement (KETAM) • Medicines Transparency Alliance (MeTA) • Medecins sans Frontieres (MSF) • Oxfam
Industry associations	<ul style="list-style-type: none"> • Federation of East African Pharmaceutical Manufacturers (FEAPM) • Southern African Generic Medicines Association (SAGMA) • West African Pharmaceutical Manufacturers Association (WAPMA) • Federation of African Pharmaceutical Manufacturers Associations (FAPMA)

4.3 PROPOSED STRUCTURE FOR DELIVERING THE PMPA

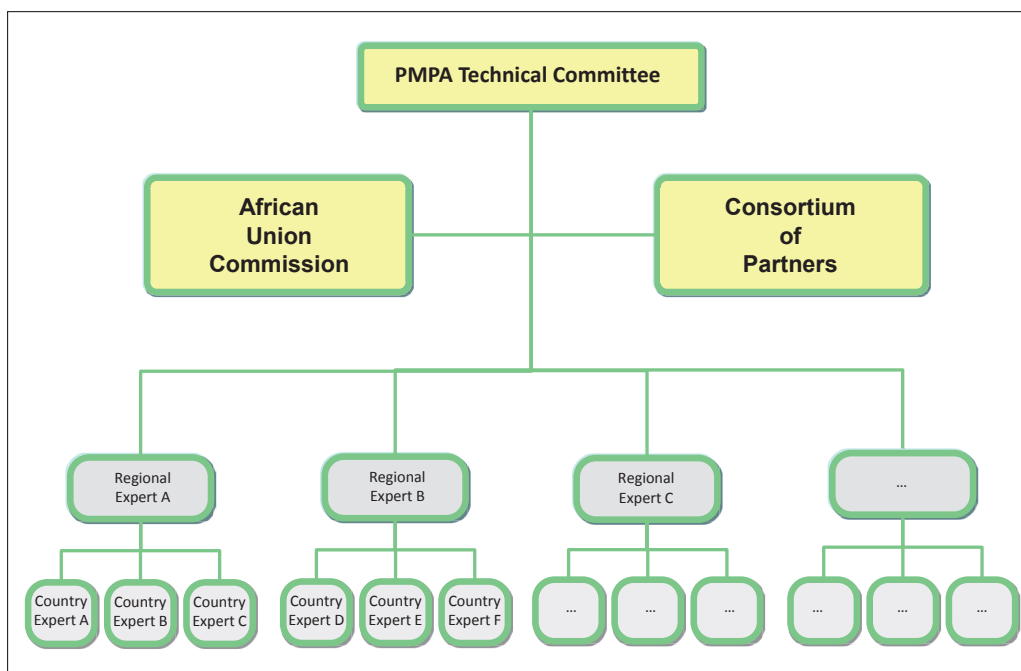
Figure 10 details a proposed structure for the PMPA. The central consortium, the coordinating roles of UNIDO and the imperative of engaging with a broader set of stakeholders are detailed elsewhere in this chapter. A further critical component of the envisaged structure is a dedicated field presence. Yet, however comprehensive and appropriate the solutions package is, true progress will only be achieved through the actual real world implementation of these aspects on the ground. Experience and historical evidence from other endeavours suggest that sustainable progress requires coordinated implementation that is dependent on the cooperation of a number of actors at the country and REC level. This is both a technical and a human challenge. In some circumstances, it will require overt leadership to instigate,

motivate, and coordinate different parties. In other instances, where initiatives are already underway, it will be imperative that the PMPA supports ongoing efforts and does not try to replicate and/or take over the agenda.

Experienced individuals with the credibility and ability to recognize and adapt to the different dynamics as well as to influence high level office bearers will be imperative for the success of the programme. It is proposed that four regional coordinators be placed in the field with responsibility for managing the implementation of the PMPA (whether as a ‘go it alone’ or as a supporting initiative) at country and regional level. They would be responsible for accessing the package of solutions from the central hub on behalf of the stakeholders in the field both at the REC level and in individual countries that have engaged the PMPA to help develop their industries.

It would not be feasible or necessarily appropriate (as capacity building for the long term should also be an objective) to engage such individuals for each and every country and national level experts would be employed to manage the administration of the solutions. The regional coordinators will provide the high level support as and when necessary. Figure 10 below gives a schematic representation of the relationships between the different aspects of the proposed structure.

Figure 10: Proposed structure for implementation of the Business Plan



Additional temporary expertise will be required and will include the pool of experts that will be recruited to offer various services to the industry and to assist the PMPA programme team when needed. This pool of experts will be assisted in the regions and at country level by the permanent team members leading the various interventions.

4.4 RESOURCE REQUIREMENTS

The AUC and UNIDO will take the lead in mobilizing the resources required to deliver this Business Plan. It is proposed that UNIDO hold a trust fund for central PMPA resources which would be disbursed to different consortium partners and the broader range of stakeholders according to the action plan developed (including identification of expertise beyond the consortium to be financed from central programme funds). The details of the resource requirements in terms of different components, timing and magnitude will be developed in line with the action plan. However, at this stage it is possible to identify the major components of the plan which will require funding and to provide some indicative figures for the overall resource requirements as well as the expected timing of those resources.

There will be some elements of fixed cost in setting up the human ‘infrastructure’ required for the Business Plan and for the operation of the central consortium. There will also be fixed costs associated with further work on developing the solutions package. In addition, there will be variable costs that will depend on the number of countries and (RECs) that actively engage with the PMPA and the level of activity required in each country. For example, the complexity of the situation in countries with well established industry sectors is likely to require more detailed and wide ranging activities at the different stages of the country level process than in a country that has limited or no pharmaceutical manufacturing.

A significant proportion of the overall cost of the Business Plan is expected to be incurred in the process of developing human resources for the pharmaceutical manufacturing system. Investment in facilities for training will be beyond the scope of the PMPA so established centres of excellence will be utilized and the PMPA will actively lobby for expanding the model of training provision, for example, at the Saint Luke Foundation. The nature of sponsorship for participants on these courses will also need to be considered. For example, UNIDO currently sponsors participants on the extended course at Saint Luke Foundation providing 50% of fees for private sector actors and 100% of fees for public sector representatives (travel and subsistence costs are covered by the individual or his/her organization). Similarly, an extensive syllabus of in-country training modules is anticipated and the degree to which these are fully funded under the PMPA or whether some fees will be recouped will need further consideration and may vary depending on the specific nature of the module and the resource requirements.

This Business Plan also proposes utilizing the expertise of research entities for the development of new formulations and for developing synthetic pathways for APIs required in products covered by patents that could be developed for production under the TRIPS flexibilities. These APIs would be used in formulations that would also need to be developed. It is envisaged that these initiatives would require initial seed funding and that their ongoing activities to develop further products would be financed by recouping the investment through charging fees to GMP-compliant companies and taking a cost sharing approach.

The following table lists the main cost components described above and provides guidance on the expected timing implications as well as, where possible, indicative figures. The total resource requirements identified in this indicative budget are roughly US\$54mn over five years, with an annual breakdown of US\$4mn, US\$16mn, US\$14mn, US\$10mn and US\$10mn in years 1 to 5 respectively.

Table 5: Indicative estimate of resource requirements for full implementation of the Business Plan

Cost Component	Timing Implications	Assumptions	Estimated magnitude
Seed funding for set up phase	First 6- 8 months of Business Plan	UNIDO will auto finance its activities in support of AUC. The Commission will require funding for travel. Consortium partners will largely cover own costs although some support may be necessary. Any legal advice will be sought from internal capacity	\$50k
Human Infrastructure: 4 Field Coordinators, additional programme management head count, additional staff requirements in central core partners (4 new staff across the institutions)	Ideally these positions would be filled during the set up phase of the programme and would be in place until the end of the first five years of the Business Plan's implementation	Estimated that 10 positions required. Lead time issues likely so assume posts filled for on average 4 of the 5 years. Relatively experienced individuals required so a figure of \$1.50k per year each is estimated.	Each individual will cost an average of \$600k over the five years with a total cost of \$6mn for all 10 'PMIPA staff'
Solution development: EML risk assessment, training syllabus, etc.	To be conducted during the set up phase ready for roll out ASAP	Major costs will involve convening of meetings. Assume 10 meetings (across different issues) with 7 expert participants at each and meetings last three days. Experts will require payment and travel. Consortium members will self fund. UNIDO will fund the development of the GMP roadmap separately	Expert costs \$500 per day, plus \$300 per day DSA plus travel at \$1,500 per round trip Total: US\$273k
Strategy development per country	Will depend on number of countries and the speed of set up. Will include recruiting a national level coordinator to escort the process. This scale up phase should be completed by middle of the 5 year time frame	Total cost per country will vary significantly. Estimate involvement in 30 countries across our continent with an 'average total cost' of the consultative process (including regular travel by regional coordinator, round tables and travel and/or fees for solution expertise presence in the field as required, GMP audit, etc.) Average US\$300k per country.	Year 1: US\$1.1mn Year 2: US\$4mn Year 3: US\$4mn Total cost for 30 countries US\$9mn
Sponsoring formal training courses	Depends on capacity of institutions and degree to which this can be enhanced. Models will probably be scaled up over the 5 year time frame	Assumes: 50 participants in 1st and 2nd year intake with 100 in 3rd, 4th and 5th. Fees per student \$6,000 for 2 year course; average of 75% cost per participant borne by PMIPA Cost per year per student covered = US\$2,250	Year 1: US\$112.5k Year 2: US\$225k Year 3: US\$337.5k Year 4: US\$450k Year 5: US\$450k Note: additional US\$225k required for second year of last intake Total: US\$1.8mn

Cost Component	Timing Implications	Assumptions	Estimated magnitude
In-country/country cluster training courses across various dimensions.	Will depend on development of syllabus and functioning of Trade Associations	Assumes: Courses in-country in 10 countries and for 4 country clusters. 20 sessions per year funded by PMPA (other training providers will augment with their own funding) with costs limited to venue, materials and travel and professional fees of trainer. Total per session US\$4k (possibility of charging fees but assumes full cost borne by PMPA). Scale up with 50% in 1st year, 75% in 2nd year and 100% in 3rd, 4th and 5th years	Year 1: US\$560k Year 2: US\$840k Year 3: US\$1.12mn Year 4: US\$1.12mn Year 5: US\$1.12mn Total: US\$4.76mn
Implementation phase TA across manufacturing system in accordance with agreed strategy	Suggested that in Ghana and Kenya implementation starts beginning 2013. Other countries begin to enter implementation phase in 2014 with all strategies in 30 countries complete by end 2015	Resource requirements for implementation support will vary widely but average estimated at US\$250k per year per country. Assume 5 years support for first two countries. A further 8 countries receive 4 years and 20 countries 3 years TA	Year 1: US\$500k Year 2: US\$2.5mn Year 3: US\$7.5mn Year 4: US\$7.5mn Year 5: US\$7.5mn Total: US\$25.5mn
New formulation development	One off payment (although could be phased), with revolving fund model	Assumes: Five entities receive seed funding in 2nd year of plan Each organisation receives 'working capital' of US\$1mn Technology transfer costs will be borne by the recipient company	Total cost in year 2: US\$5mn
Business linkages platform	Dedicated PMPA staff member (included above) but annual operating costs will relate to staff travel and PR activities. Assume one partnering event in 2nd and 4th years	Will include a web portal managed by central PMPA staff. Marketing of service required so PMPA staff to travel to conferences for awareness building. 5 conferences per year at US\$6k each. Also travel to BRICS countries and Europe for promotion of service - 3 trips per year at US\$8k per trip Event in year 2 and 4 at US\$150k each.	Year 1: US\$54k Year 2: US\$204k Year 3: US \$54k Year 4: US\$204k Year 5: US\$54k Total: US\$570k

Cost Component	Timing Implications	Assumptions	Estimated magnitude
PMMPA stakeholder events	One event during the set up phase: one in year 3 and one in year 5. Ongoing dialogue will be conducted by core PMMPA staff to maintain communication	Each event US\$ 150k	Year 1: US\$ 150k Year 2: US\$0 Year 3: US\$ 150k Year 4: US\$0 Year 5: US\$ 150k Total: US\$450k
Technical Committee meetings	Annual meetings of the Technical Committee will take place, plus an exceptional meeting expected for approval of action plan half way through year 1.	2 day meetings with simultaneous translation, facilities and travel for TC members and PMMPA staff covered. Assume 20 TC members per event, with costs per individual US\$2.5k. Plus facilities etc. US\$ 10k per event	Year 1: US\$ 120k Year 2: US\$60k Year 3: US\$60k Year 4: US\$60k Year 5: US\$60k Total: US\$360,000
Consortium meetings	Regular meetings of the consortium are expected to take place every six months and in the set up phase will be self financed. When resources mobilized, costs should be covered by PMMPA	Assume 10 travelling participants with venue changing but average cost of \$2.5k per travelling participant	Year 1: US\$50k Year 2: US\$50k Year 3: US\$50k Year 4: US\$50k Year 5: US\$50k Total: US\$250k
Support to leading companies to achieve prequalification	Weighted towards the first half of the Business Plan	Assistance dependent on specific needs of company but based on technical assistance not capital investment. Assume 10 companies benefit and each company receives support equivalent to US\$200k spread over first 2 years	Year 1: US\$ 1mn Year 2: US\$ 1mn Total: US\$2mn
Ongoing research into dimensions of pharma manufacturing system and continental strategy development for API production, traditional medicines, etc. (note: blood product work being conducted separately by WHO. Findings could be incorporated under PMMPA as additional activity but not included in this indicative budget)	Research function has consistent annual budget that starts in year 2.	Dedicated PMMPA staff member to manage research activities; will require expert consultancies and expert group meetings. Suggested budget of US\$250k per year:	Year 1: US\$0 Year 2: US\$250k Year 3: US\$250k Year 4: US\$250k Year 5: US\$250k Total: US\$ 1mn

4.5 MONITORING AND EVALUATION

It would be premature to provide a detailed logical framework for the PMPA as the specific activities to be conducted are subject to a number of variables including the detailed outcome of discussions on the agreed action plan. That plan will include specific activities to be undertaken by each party and metrics for assessing progress. However, a Monitoring and Evaluation (M & E) philosophy, indicative key objectives and possible means by which progress can be measured are identified in this section based on the fundamental objectives of the PMPA as articulated in the first section of this Business Plan.

The key objectives should form the basis of an approach to monitoring and evaluation which should take into account that:

- This programme is intended to benefit all member states
- The quality of pharmaceutical production should be raised to international GMP standards and ultimately it should be a non-negotiable requirement that manufacturers must meet if they are to supply our people
- There is a need to expand the range of drugs that our manufacturers produce (subject to the manufacturer meeting international GMP standards)
- The industry must be sustainable in the long term and competitive whilst operating to international standards
- NMRA's will be advised to limit the range of products that companies can produce unless they meet GMP requirements
- There is a need to develop and implement coordinated strategies at the national level
- A fundamental long term requirement is that regulatory capacity is strengthened and that, in resource constrained environments, efforts are targeted at those aspects of regulatory activities that are critical to protecting public health
- Some of our more advanced member states have well developed manufacturing systems but wish to reduce their reliance on imports and possibly develop/expand their export markets to include those overseen by stringent regulatory authorities
- We have some companies that are prequalified for manufacture of products by WHO and/or other stringent regulatory authorities and there are others who are striving to achieve this milestone. We need to increase the number of internationally certified products from African manufacturers (increased number of manufacturers and broader product range)

This Business Plan underlines the fact that the different countries on our continent currently face a diverse range of realities. In view of this, the M & E approach should report information at the national level as well as at continent level so that a true picture of the progress in diverse situations is not lost through amalgamation of results at the continent level. National level data will be a necessary component of strategy design and implementation in individual member states and it is important that this level of detail is also reflected in the overarching M & E for the PMPA.

Based on these observations, the following table identifies putative measures by which the progress and success of the PMPA can be monitored. It describes a possible indicator and provides a brief description of the rationale behind the indicator identifying the dimension that it covers and limitations if individual indicators are considered in isolation.

Table 6: Potential indicators for national and continent level M & E

<i>Indicator</i>	<i>Rationale and Limitations</i>
Proportion (value and volume) of pharmaceutical market supplied by Africa-based manufacturers.	Would indicate sustainability of production as market share will to some extent be a function of affordability. Increased market share in certain product categories could be broken down to look at increased range of product portfolios. The degree to which NMRAs enforce limitations on production portfolios prior to GMP compliance means that a strong performance on this indicator could represent insufficient regulatory sanction and therefore must be considered together with other indicators relating to quality.
Proportion of products in the market place that are found to be sub-standard and the severity of the non-conformity with requisite parameters	The intention of the PMPA is that we should be able to rely more heavily on our own industry for high quality drugs to reduce reliance on imports which often cannot properly be overseen by our NMRAs. Will require an initial baseline survey. Important to capture the nature of deviation as well, since a 'pass/fail' binary measurement may miss improvements that would be captured if the trend is for the proportion of failures due to less significant issues to increase.
Number of companies achieving WHO prequalification of a product or certification by a stringent regulatory authority and number of products for which certification achieved	Indicator would capture progress of leading companies towards achieving goals to supply international donor markets and, for more advanced countries, would capture progress in penetrating developed world export markets.
Proportion of products procured by international donors sourced from Africa-based manufacturers	Companies need to fill orders if their investment is to pay dividends. Would speak to the competitiveness of manufacturers although the degree to which incentives/support contribute to this will be relevant with regard to long term sustainability. Definition of proportion (value/volume/treatment courses) will need to be considered.
Improved Capacity of National Medicines Regulatory Authorities	Regulatory authority functions go beyond the specifics of local production and central to the PMPA is overall improvement in quality and access. Need to ensure that the PMPA does not unintentionally distort NMRA efforts to make maximum use of limited resources in protecting public health.
Number of National Quality Control Laboratories prequalified by WHO	An indicator that could provide a proxy for improved regulatory capacity but which should be considered in the context of wider regulatory infrastructure requirements for market oversight, etc.

Number of countries that have developed and are implementing strategies	Implicit assumption that a strategy has been developed through consensus building and that there is detailed engagement of all stakeholders as the presence of a strategy alone does not measure the value of the approach.
Amount of capital investment in pharmaceutical manufacturing activities	A proxy measure for the credibility of the ongoing progress of the sector and its future viability as providers of capital will weigh risks such as threat from counterfeit and sub-standard products in their investment decisions.
Number of countries amending legislation to incorporate TRIPS flexibilities and the number of products on the market as a result of exploiting the flexibilities and price of products versus originators	TRIPS flexibilities represent an important opportunity for improving public health and incorporating the legislation is one step; but the degree to which this translates into availability of affordable versions of patent protected products in Least Developed Countries (LDCs) on our continent should also be captured. The measure of 'price' needs careful consideration to ensure that a genuine comparison is made.
Number of industry professionals trained across different disciplines required by the pharmaceutical manufacturing system	Human resource development is key and empirical evidence of progress can be captured through this indicator; however, the ability of those trained to effect change in their respective organisations will also depend on intangible aspects such as changing 'culture' of the organisation which is implicit in a number of metrics related to quality and competitiveness.
Number of Partnerships and Business Linkages facilitated	The Partnership and Business Linkages Platform will cover a diverse range of possible relationships. The impact of the PMPA is intended to adjust the operating context of the industry to make it more attractive to investors and encourage partnerships, etc. An appropriate metric to capture this diversity and the indirect impact of the PMPA will require further deliberation.
Emergence of supportive industries	Appearance of local industries that, for example, manufacture excipients and packaging material and are able to service and retool equipment. These supportive industries will be essential for the long term sustainability and competitiveness of our pharmaceutical manufacturers.

4.6 RISK MANAGEMENT

This section reviews some key considerations and assumptions about the programme, identifies potential risks for the successful implementation of the PMPA, and presents a risk mitigation strategy including the necessary legal agreements and provisions and protections, as well as the management and control of programme funds.

The AUC is acutely aware that implementing a programme of this nature, with the myriad of contexts on the continent, and the various ambitions and stages of development of companies, is a challenging undertaking. This is especially so because most interventions will be carried out by partners who have their own governance and internal dynamics. The potential risks to the success of the PMPA implementation therefore derive from the following:

- The risk that external players do not align behind the PMPA given that uncoordinated vertical programmes can create distortions
- Interactions with stakeholders will lead to the evolution of the programme, the addition of new partners, the expansion of the package of solutions, and result in modifications of partner roles. Some may find the increasing or reducing responsibility unacceptable
- The challenge of a number of organisations engaging in genuine collaboration and maintaining this over the long term
- Funding shortfalls leading to the abandonment of some key interventions or even the inability to commence PMPA implementation

Ways in which the above risks can be mitigated include:

- Continuous stakeholder interactions and consultations
- Continuous monitoring and evaluation of project implementation and reporting to ensure that adjustments and corrective actions are taken or that interventions that do not work are abandoned
- Open communication and reporting to the AUC PMPA Technical Committee and all partners and stakeholders so that they are kept abreast of all developments
- Regular coordination meetings
- Governance and controls should be in place and should regulate all aspects of programme management, including use of financial resources

4.7 SUMMARY OF CHAPTER 4

Key messages from this Chapter include:

- The implementation of this Business Plan will require a diverse range of skills, expertise and organisational mandates; no one entity can cover them all
- It is recommended that a consortium is established and genuine collaboration between partners will be essential
- UNIDO has been requested to assist the AUC to build the consortium
- Initial discussions have taken place with potential partners; during the initial phase of the Business Plan, detailed negotiations will take place, legal arrangements will be

established and the consortium will work together to establish a detailed work plan

- The initial or ‘set up’ phase of this Business Plan will also involve further development of the solutions package, resource mobilization and an invitation to our member states to express interest in working with the AUC and its partners under the PMPA
- The consortium will of necessity be limited in size so inevitably there will be many stakeholders who are conducting related work and with whom collaboration and alignment with the PMPA will be important. In view of this, the AUC and its partners will ensure during implementation that channels of communication with the wide array of players are kept open and that there are opportunities for regular face-to-face-interaction
- A pilot phase is suggested as there are a number of countries that have already developed strategies for the sector and who would be in a position to benefit from detailed implementation by the consortium
- Prior to implementation in other countries, a detailed strategy development process will be conducted in each one (as described in Chapter 3) prior to full scale implementation
- Experience suggests that coordination across stakeholders at the national level is necessary and an implementation structure that includes dedicated PMPA field coordinators is recommended
- A complete budget proposal for the implementation of the Business Plan will depend on the details of the action plan to be developed by the consortium partners. However, an indicative budget is proposed which estimates that over a five year period US\$54mn will be required
- Indicative indicators have been suggested and the rationale and limitations of these indicators discussed. A detailed logical framework will be produced to capture the details of the action plan and the measures by which it will be monitored and evaluated
- Risks to the effectiveness of this Business Plan are highlighted and include the challenge of maintaining a functioning consortium of parties over an extended period of time. This is an issue that will benefit from continuous dialogue, regular meetings and monitoring and evaluation activities.



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