U. S. Pharmacopeia Drug Quality and Information

Review and Assessment of Drug Quality Assurance and Control in Madagascar

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Note to Readers

Data and information presented in this Report reflect the data and information found from both primary and secondary sources, including Ministry of Health (MOH), Agence du Médicament de Madagascar (AMM) publications, and reports provided to the Assessment Team by correspondents during the review and assessment visit October 12-18, 2003

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Acronyms and Abbreviations

AFSSAPS	Agence Française pour la Sécurité Sanitaire des Produits de Santé (French Agency for Health Safety of Health Products)
AMM	Agence du Médicament de Madagascar
API	Active pharmaceutical ingredient
BP	British Pharmacopoeia
DPL	Direction des Pharmacies et Laboratoires (Department of Pharmacies and Laboratories)
DRA	Drug regulatory authority or agency
EP	European Pharmacopoeia
EU	European Union
FC	French Cooperation
FE	Fonds Européen de Dévelopement (European Funds for Development)
FMG	Franc Malgach -local currency
GMP	Good manufacturing practices
HPLC	High performance (or pressure) liquid chromatography
IMRA	Institut Malgach des Recherches Appliquées (Applied Research Institute of Madagascar)
Int.P	International Pharmacopoeia
LNCQM	Laboratoire National de Contrôle de Qualité des Médicaments (National Laboratory for Drug Quality Control)
MOH	Ministry of Health
MSH	Management Sciences for Health
PSI	Population Services International
QA/QC	Quality assurance and quality control
RPM Plus	Rational Pharmaceutical Management Plus Program
USAID	United States Agency for International Development
USP	United States Pharmacopeia
UV	Ultraviolet spectrophotometry
WHO	World Health Organization

Executive Summary

Drs. Souly Phanouvong and Abdelkrim Smine from USP DQI visited Madagascar the week of October 13-17, 2003, to assess the country's drug quality assurance program and quality control system. The Director of the Drug Regulatory Authority of Madagascar, known as Agence du Médicament de Madagascar (AMM), and USAID/ Madagascar coordinated the visit. A specially designed assessment tool, developed by USP DQI, served as the basis for the assessment.

The objectives of the evaluation were:

1. To assess how the existing drug regulatory authority functions;
2. To identify strengths and weaknesses of the country's drug quality assurance program and quality control systems; and
3. To make suggestions and recommendations to policy-makers, decision-makers, and authorities responsible for designing and developing appropriate drug QA/QC systems adaptable to their political and socio-economic conditions.

Both national (government drug industry, private drug companies, research institutes, and procurement agents) and international (WHO, World Bank, UNICEF, and PSI) agencies involved in pharmaceutical management including production, manufacture, importation, procurement, distribution, utilization, and donation, were consulted. (See Attachment 1 - Program Agenda.) The Ministry of Health, the Cabinet of the Health Minister, the AMM, and the Direction for Pharmacies and Laboratories endorsed the purpose of the visit.

During their visit, Drs. Phanouvong and Smine (the Assessment Team) determined that the Ministry of Health strongly supports efforts to improve Madagascar's QA/AC systems. Likewise, the AMM staff wishes to ensure that the medicines they control are of good quality. The Agence, in fact, began initiating inspection and registration services in 1995, despite its small size and limited resources. AMM activities were boosted by the aid of laboratory equipment from the European Union and the Government of France. The Assessment Team acknowledged their efforts and reports these findings:

- Absence of drug quality control system in the country
- The AMM lab is not functional; it needs equipment, staffing, and training.
- Drug registration and inspection system is very weak.
- No GMP compliance exists by local manufacturer.
- Lack of drug regulations and National Drug Policy
- Availability of local scientific resources
- Strong commitment to improve drug quality control systems at all level

USP DQI can best contribute to the Madagascar quality improvement efforts by providing technical assistance and training. Laboratory personnel need advanced training in Good Laboratory Practices, laboratory management, documentation, and basic testing methods; field personnel require training in modern registration methods, inspection sampling techniques, and post-marketing surveillance. Of the first priority, however, the AMM will need to increase

the number of lab staff to strengthen the capacity of the AMM Laboratory for Drug Quality Control.

USP DQI might also assist the Madagascar Ministry in structuring a national drug policy that will legalize and regulate all aspects of QA and QC of essential drugs and clearly indicate the responsibilities of each agency involved. An improved set of guidelines and improved communications among the leadership and field staff will strengthen the QA/QC system and help Madagascar to sustain the program in the future.

1. Introduction

Medicines form an important component in any health care system. They must be safe, efficacious, and of good quality in order to produce the desired therapeutic effects. Problems related to the quality and safety of medicines are becoming an increasing concern in many places around the world, especially in developing countries. Adequate drug legislation and regulation — and their effective enforcement, a competent drug regulatory authority, and appropriate drug information are required to ensure the safety, efficacy, and high quality of medicines.[1]

Legal structures are the foundation of drug regulation. In some countries, drug laws may not cover all critical aspects of pharmaceutical activity, for example, the local producers of certain drugs for domestic use may not be required to comply with good manufacturing practices (GMP). Clinical study data may not be required to register the drug for sale. Many drug regulatory agencies (DRAs) do not provide documented standard procedures for registration; others have no written guidelines or checklists for inspection.[2] All of these factors and others, have resulted in regulatory gaps and inconsistent enforcement of laws.[3] [4]

All DRA functions must work together in order to provide effective public health protection. Key functions are licensing, product quality assessment and registration, inspection of manufacturing facilities and supply channels, laboratory testing, and post-marketing surveillance for quality, adverse drug reactions, and guidelines for drug promotion and advertisements.[5]

2. Objectives of the Review and Assessment

The Madagascar Ministry of Health, familiar with USP's established reputation of promoting public health through developing and disseminating pharmaceutical monographs and reference standards, approached the organization through USAID to review and assess their country's drug quality assurance and drug quality control systems. The objective of the mission was to study the current QA/QC situation and make suggestions to bring AMM's Laboratory functioning up to standards. To achieve this goal, the Assessment Team specifically designed and planned the assessment to:

1. Determine whether or not the DRA in Madagascar is functional;
2. Examine what approaches and what mechanisms the country uses to ensure the quality of pharmaceuticals sold there and, if directed by a drug regulatory agency, how the DRA carries out its responsibilities;
3. Identify strengths and weaknesses of the country's drug quality assurance program and quality control systems and determine the reasons for them;
4. Make suggestions and, where appropriate, recommendations to policy makers, decision-makers, and responsible authorities for designing and developing appropriate drug QA/QC systems adaptable to their political and socio-economical conditions.

3. Assessment Methodology

3.1. Design and tool

The methodology of this assessment was based on the following framework:

- Pre-marketing quality assessment – which includes licensing of pharmaceutical establishments and product quality assessment for registration;
- Regulatory functions – covers central administration, quality control or testing and inspection services, and product recall.
- Technical elements – deals with norms, standards, specifications and procedures, and good practices.
- Post-marketing surveillance – covers monitoring for drug quality and adverse drug reactions, and control of drug promotion and advertising.

3.2. Preparation and data collection

The process for reviewing and assessing the Madagascar drug QA program and drug QC system is illustrated below. (See Figure 1.)

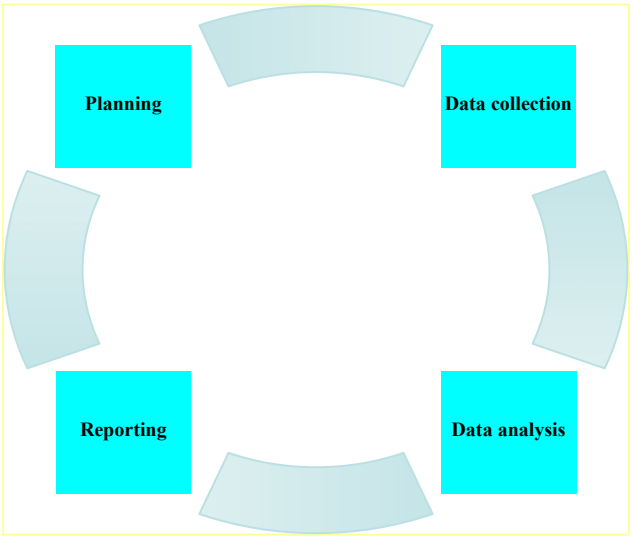


Figure 1: Review and assessment process

A pre-defined indicatory questionnaire was used to collect the data and the information required for the review and assessment. (See Annex.) Data collection was carried out using combined techniques, namely:

1. Conducting formal or semi-formal discussions and consulting with key officials of MOH, directors or deputies of Agence du Médicament de Madagascar (AMM), chiefs of divisions within the AMM, the government drug manufacturer (OFAFA – a local public enterprise), the World Bank, Population Services International (PSI), UNICEF, WHO, Institut Malgach des Recherches Appliquées (Applied Research Institute of Madagascar), a private drug producer (FARMAD), the AMM Drug Testing Laboratory, Direction of Pharmacies and Laboratories, the government procurement/wholesale agency - Salama, and the Central Medical Store for Essential Medicines and Medical Materials.

2. Studying and reviewing relevant and accessible (both published and unpublished) technical documents and records from primary and secondary sources. This includes drug laws, executive orders, inspection records, DRA and National Laboratory for Drug Quality Control annual or mid-term reports, and health and drug related indicators.

3. Using other convenient techniques, such as email, fax, and telephone.

3.3. Methods for data analysis and reporting

Quantitative data collected for each question or obtained from other techniques were examined, analyzed, and computed into percentages (where appropriate). Where necessary and appropriate, these data were presented in graphs or tables for better understanding.

Relationships between certain constructs of data were identified to find possible explanations for evaluation of a drug regulatory system technical and managerial capability and, possibly, DRA performance.

Each relevant data set representing each aspect of the country's drug quality assurance and control framework — including pre-marketing quality assessment, regulatory functions performance, technical components, and post-marketing surveillance — were analyzed and used in an effort to explain "how" and "why" each aspect "works" or "does not work."

The analysis and report were rendered based upon the principles in Figure 2 below.

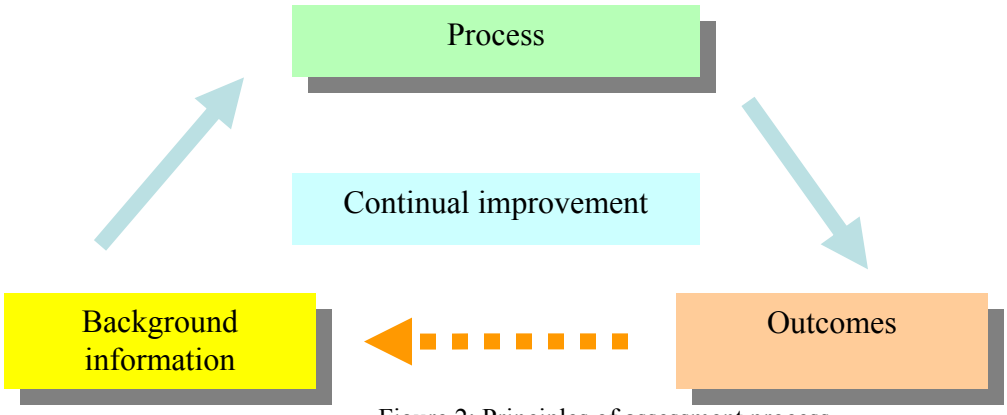


Figure 2: Principles of assessment process

- Background information - covers brief background information on demographic, economic, health, and pharmaceutical (with key indicators on health and pharmaceutical services of both the public and private sectors, drug regulatory system, drug quality assurance and control), and specific data on drug regulatory functions.

- Process – reflects the mechanisms and activities by which a DRA performs. Process indicators are used to assess the effectiveness of these mechanisms and activities, in particular, legislation, regulation and enforcement of drug laws, selection and registration of essential medicines, and allocation of human and financial resources for various drug

regulatory activities (e.g., product quality assessment, registration, inspection, testing, and continuing education).

- Outcomes – attempts to present the achievement of common objectives of a functional DRA. The objectives include: Adequate mechanism for drug registration; effective inspection services; availability and use of established national or international standards for quality, safety and efficacy; specifications and practices; and competent laboratory services. Outcome indicators are used to demonstrate the degree to which these objectives are being met. Outcomes are usually measured against the set targets described in the development plan of the DRA.

- Continual improvement – denotes the overall goal for all the efforts made by the government and its respective ministries and departments, including the Ministry of Health, the Drug Regulatory Authority, and other key players, to achieve and maintain.

4. Country Background on Health and Pharmaceutical Services

Madagascar is an island located off the East Coast of South Africa and Mozambique. It has a population of 15.5 million people (2000 est.) 26% of whom live in an urban area while 74% live in rural areas.[6] Road access to villages remains a major concern and often limits or denies the rural population access to public health facilities, including medicines. Madagascar faces problems of chronic malnutrition and under-funded health and education facilities. The average life expectancy of a Madagascar citizen at birth is 54.9 years (2000), the average per capita income 780 US$ (1999 est.). Agriculture, including fishing and forestry, is the mainstay of the economy, accounting for 34% of the country's Gross Domestic Product (GDP) and contributing more than 70% to export earnings[7]. French and Malagasy are official languages.

The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) has approved two project applications for Madagascar. One project, "Expanding access and use of sexually transmitted infections diagnosis and treatment services in Madagascar - a primary AIDS prevention strategy," was awarded an initial grant of $747,199.00 over two years. The second project, on the prevention of malaria with a grant of $1,482,576.00 over two years, aims at increasing access and use of insecticide-treated nets through a social-marketing approach. Population Services International (PSI) is implementing the project in collaboration with the MOH.

Malaria is the major cause of morbidity and mortality in Madagascar. Three-quarters of the population live in endemic areas (mainly along the East and West Coasts) and one-quarter live in epidemic zones (mainly in the Central Highlands and Southern zones). In the epidemic zones, a sentinel surveillance system operates to alert health facilities to malaria outbreaks. The main parasite is *Plasmodium falciparum*. Chloroquine is still effective (at 18% resistance) and is considered the first-line drug.[8] Tables 1-5 present some selected health and health system data.

Table 1: Selected data on health of Madagascar

Description	Number and Year

Child mortality rate (per 1000 live-birth)	148.5 (2001)*
Maternal mortality rate (per 100,000)	488 (1997)
Per capita government expenditure on health	6 US$ (2000)**
Government vs. private expenditure on health	71.8% vs. 28.2%**
Total value of international aid for health sector	7, 100,000 US$ (2002)

Source: Agence du Médicament de Madagascar Ministry of Health.
* WHO. WHO statistics/country compare. Comparison on selected indicator within WHO Region. http://www3.who.int/whosis/country/compare.cfm?language=english&country=mdg&indicator=strMortChildMale2001,strMortChildFemale2001
**WHO. Selected health indicators. http://216.239.39.104/search?q=cache:O7ZbsEDnm04J:www3.who.int/whosis/country/indicators.cfm%3Fcountry%3Dmdg+government+health+expenditure+madagascar&hl=en&ie=UTF-8

Table 2: Number of health facilities in the country, 2002

Health facilities	Government/Public	Private
Central/teaching hospital	2	1
Regional hospital	4	2
District hospital	99	11
Health center (2000)	2131	250

Source: Data provided by Agence du Médicament de Madagascar Ministry of Health.

According to the Madagascar Ministry of Health, equitable access to medicines, even essential medicines, remains a major issue of concern for the Government to address. Madagascar relies substantially on the private sector for its pharmaceutical services. The majority of pharmaceutical establishments, including wholesalers, pharmacies, and small retailers are concentrated in the urban commercial areas, especially in Antananarivo and Fianarantsoa provinces.

Table 3: Selected data on Madagascar pharmaceutical sector

Total government pharmaceutical expenditure, in US$	3,571,500 (2002)
Per capita drug expenditure, in US$	0.38 (2000)
Total value of domestic pharmaceutical production, in US$	3,294,500 (2001)
Total value of imports of finished drug products, in US$	19,089,000
Total value of imports of APIs, in US$	No data
Total value of exports of finished drug products, in US$	0

Source: Data provided by Agence du Médicament de Madagascar Ministry of Health).

Table 4: Country health and pharmaceutical human resources

Description		Number in 2003
Type and number of health professional training schools		
	Medical	2
	Pharmacy	0
	Others, e.g., dentistry, nursing	1 (dentistry) 2 Nursing
Number of health professionals		
	Total number of medical doctors	1524 (10170 inh./doctor)
	Total number of pharmacists	248 (62500 inh./pharmacist) (2002)

Source: Data provided by Agence du Médicament de Madagascar Ministry of Health.

Table 5: The status of pharmaceutical sector in 2002.

No. of establishments		Government	Private
Pharmaceutical manufacturing plants		1	2
	For APIs	0	0
	For finished dosage forms	1	2
	For packaging finished dosage forms	0	0
Research-based pharmaceutical industry		1*	1*
Pharmaceutical importers/wholesalers		1	23
Pharmacies		0	203
Small retail-drug outlets (dépôts de médicaments)		0	1625

Source: Data provided by Agence du Médicament de Madagascar Ministry of Health.
Note: * a small-scale research activity on traditional medicines only.

5. Current Drug Quality Assurance and Control System

As in many other developing countries, the Madagascar drug quality assurance program is in its infancy and requires both technical and managerial capacity strengthening. Prior to 1980, Madagascar imported most medicines from France or the European Union (EU) and their quality was assured by the regulatory authorities in exporting countries.[10] Due to changes in economic policy, most medicines (particularly generic products) are imported from different sources, such as India and China, where the quality is less certain. Low cost has been a main consideration for drug procurement practice. The Agence du Médicament de Madagascar, the National Drug Regulatory Agency created in 1998 with the financial and technical support from the French Government (through Coopération Française), is becoming increasingly concerned about the quality of both locally produced and imported drugs.

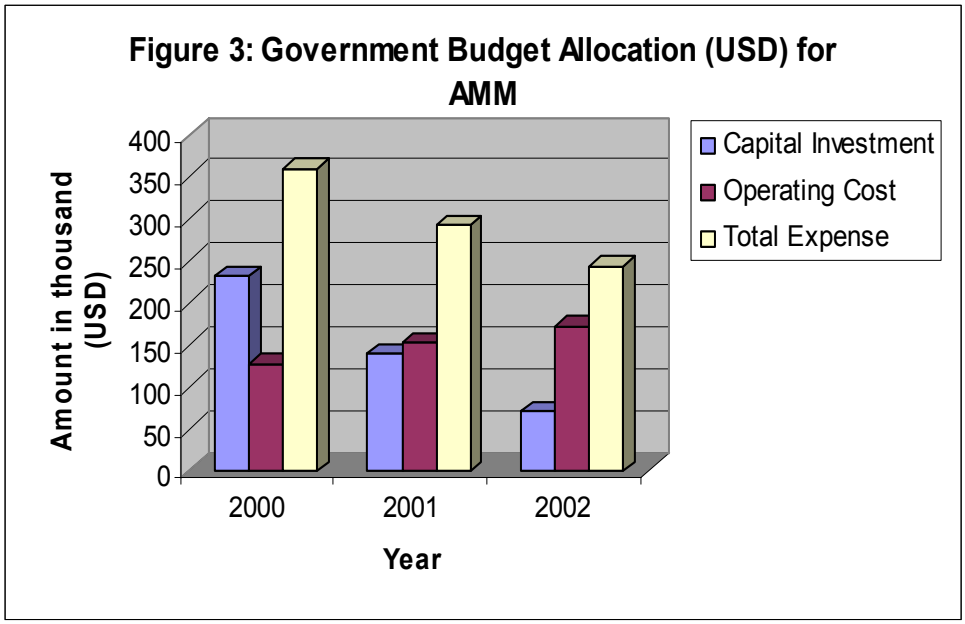
Due to limited access to information sources, it is unclear whether or not a drug law exists in Madagascar; it would appear that there are only texts and decrees that have been never enacted as law. The documents made available to the Assessment Team were a compilation of legislative papers – Recueil de textes legislatifs et reglementaires – which contain various Ministerial decrees (ordinance – French term) concerning the creation of the AMM and different aspects of drug regulation. For example, Ordinance No.62-072 of 29/09/62 concerning public health and drugs covers drug registration and production, pharmaceutical establishment licensing, inspection, drug promotion and advertising, and drug quality testing/control. It does not cover control of drug exportation, nor clinical trials and herbal/traditional medicines.[9]

Agence du Médicament de Madagascar (AMM) serves four key basic functions:

- drug registration;
- inspection;
- drug quality control; and
- pharmacovigillance.

It is interesting to note that the AMM is not mandated to regulate or deal with licensing of pharmaceutical establishments. It has neither mandate nor competence to control blood, organs, tissues, cellules, and food products.[10]

The overall Government financial allocation for the AMM has been decreasing, although the operating budget increased slightly from 860,589,000 FMG (approximately US$ 154,000) in 2001 to 974,560,000 FMG (~US$ 174,000). (See Figure 3.)



Source: AMM, 2003. Activity Report (Rapport d'activités) 1999-2002.

The AMM employees 14 professional staff; their qualifications and responsibilities are detailed in Tables 7 and 8).

Table 7: AMM professional qualifications, 2003.

Qualification	Pharmacy/ pharmaceutical sciences	Medical Sciences	Other
Post-graduates	6	5	1
Graduates			1
Technicians			1
Other (specify)			12

Source: Data provided by Agence du Médicament de Madagascar Ministry of Health.

Table 8: AMM professional staff responsibilities/functions, 2003.

Function	Post-graduates	Other (specify)
Drug product assessment and registration	1	
Licensing		This function is not under AMM mandate
Inspection	3	

Post-marketing surveillance	1	

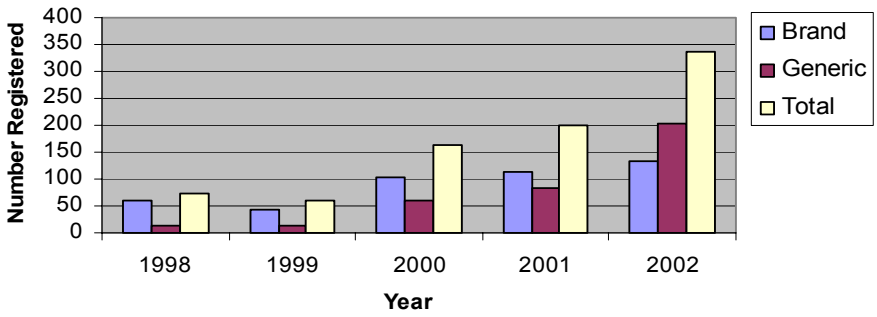
Source: Data provided by Agence du Médicament de Madagascar Ministry of Health.

Various commissions oversee the activities concerning pharmaceuticals in Madagascar: National Commission for Control of Pharmaceutical Promotion and Advertisement, National Ethics Committee for Research on Human Biomedicals, and National Drug Registration Commission.

5.1. Drug registration

Before 1998, drug registration was discharged by the Department of Pharmacies and Laboratories (Direction des Pharmacies et Laboratoires) with technical assistance from the French Cooperation. Registration was issued by the Ministry of Health. A total of 2,394 drug products were registered in the country, primarily from Europe. By yearend 2002, there were 2,114 products registered. The decrease in number of 2002 compare to that before 1998 is that many suppliers stopped marketing their products and their registration (marketing authorization) was not renewed. Figure 4 shows the evolution of drug registration in Madagascar from 1998 to 2002.[10]

Figure 4: Evolution of Drug Registration by Year



Between 1998- 2002, AMM registered 833 products

Source: AMM, 2003. Activity Report (Rapport d'activités) 1999-2002.

Currently, the Registration Service Division of the AMM, which consists of just one staff member, served as Secretariat to National Drug Registration Commission (DRC). The Registration Service is responsible for receiving and preparing the dossier for applications to register for the marketing authorization (MA) of medicines for human use. The dossier is then submitted to the DRC (Commission Nationale de l'Enregistrement des Médicaments) who decide whether or not to approve. The Commission is chaired by the Director of AMM, and consists of Director of Direction des Pharmacies and Laboratoires, a designated pharmacist from the National Board of Pharmacists, and Chiefs of the Drug Registration Service and the Drug Quality Control Lab. The marketing authorization is valid for five years. A 1998 manual on registration procedure is made available to drug importers. Manufacturers, and individuals wishing to market a drug product in Madagascar. During the assessment visit, however, many

people involved importation and/or supply of pharmaceuticals and vaccines in this country seemed to know about the manual.

Unregistered drug products, including donated drugs, are also available for use in the country; importation of these products is still allowed by the AMM and/or DPL. The AMM does not control everything that comes in the country. According to the staff responsible to Drug Registration Division, the AMM was attempting to require that all drug products be registered by November 15, 2003, with the exception of donated drugs which usually under the control of the Direction des Pharmacies et Laboratoires.

AMM registration requirements include all basic documents on the drug product, quality, safety, and efficacy. The WHO-type certificates of pharmaceutical product and GMP certificate have been used; data on clinical studies is not a key requirement. Information of whether the drug product is registered in other countries is also required. The average fee for drug registration is about US$ 225; approval time averages two to three months. Medicines to be used in the national disease programs and essential medicines for emergency in disease epidemic situations can be put on a fast-tract registration.

Key findings concerning drug registration service:

- Insufficient number of staff responsible for and performing this service (during the visit in Oct 2003, there was only one staff member).
- Very limited access to objective/unbiased information on drug quality, efficacy, and safety to compare what is provided by the applicants/ producers/suppliers in terms of reliability and validity of data and information. As such drug assessment for registration relies mostly on data/information provided by the applicants, the DRC assigns who reviews the scientific data and decides on marketing authorization.
- Advanced training in drug quality assessment and registration is needed for effective registration and to improve service, e.g., computer-assisted drug registration.
- Existence of gaps in “law or legislation” concerning drug registration which present administrative and regulatory difficulties for the AMM.

5.2. Laboratory testing

Agence du Médicament de Madagascar has its own laboratory (Laboratoire National de Contrôle de Qualité des Médicaments (LNCQM)) which currently has only one division (Physico-chemical) and is not fully functional to perform its tasks. Many factors contribute to the Laboratoire’s incapacity, including the lack of available chemical reagents and very limited laboratory personnel. The LNCQD was established in 2001 with the assistance of the French Cooperation and the World Health Organization (WHO). Since then the Madagascar Ministry of Health, with the financial and technical support of the European Union, has invested in placing some fundamental equipment and instruments. (See Table 9.)

Table 9: Availability of lab equipment/instruments at LNCQD, as Oct 2003.

Description of equipment/ instrument	Model/ Type	Quantity	Year Introduced	Functioning Status

Isocratic liquid chromatograph with UV Visible detector, manual injector and integrator	Thermo spectra series 100	1	2001	Working - requires calibration
Ultrasonic bath	Branson 3150	1	2001	Working
UV Visible spectrophotometer	Thermo Spectronic Helios Alpha	1	2001	Working - requires calibration
HPLC solvent filtration apparatus	Millipore	1	2001	Working
Forced fan oven	France etuves XU 125	1	2003	Working
UV Lamp	UVO UV GL-15	1	2001	Working
Magnetic stirrer-heater	RS 1	2	2003	Working
Dissolution tester	Erweka DT 700 HH	1	2001	Working - requires calibration
pH meter	Mettler Toledo MP 220	1	2003	Working
Orbital test tube shaker	Ika MS 1	1	2003	Working
Flame photometer	Sherwood 410	1	2001	Working
Disintegration tester	Erweka ZT 501	1	2001	Working - requires calibration
Water purifier	Purite select analyst HP 80	1	2001	Working
Analytical balance	KERN 770-14	1	2001	Working - requires calibration
Water bath	Prolabo Selecta	1	2003	Working
Digital thermometer	Hanna checktemp 2	1	2001	Working

Source: Data provided by Agence du Médicament de Madagascar Ministry of Health.

The LNCQD suffers severely from the shortage of professionals both for laboratory management, including good laboratory practice, and routine testing. Currently, there are only three professional staff members: one pharmacist, one chemist, and one laboratory-technical assistant. This Lab is able to perform some basic tests for solid dosage forms (some identification tests, loss on drying, residue on ignition, disintegration, and dissolution), some simple assay tests for some APIs, ordinary impurities and heavy metals. In 2003, however, the Lab tested only two drug samples.

The following pharmacopeias are officially accepted for drug testing: International Pharmacopoeia (Int. P), European Pharmacopoeia (EP), United States Pharmacopeia (USP), and British Pharmacopoeia (BP). The Lab claimed that it can test about 200 samples per year. Samples were sent from Government Wholesaler SALAMA, paying a fee for service of US$100 per sample.

Since its inception, the LNCQD has been financially and technically (in part) supported by French Cooperation, Agence Française pour la Sécurité Sanitaire des Produits de Santé, European Union (Fonds Européen de Dévelopement), and WHO.

Key findings concerning the LNCQD:

- Insufficient number of professional staff as well as laboratory technicians.
- Limited government budget to support the operations of the lab.
- Lack of skills and continuing education or training.
- Limited number of adequate lab equipment or instruments.

- Unavailability of certain reference standards or substances, reagents, solvents, and testing indicators.
- Limited availability of pharmacopeial specifications.
- The lab has never participated in national or international assessment for professional and technical competency, and no agency from neighboring countries has requested any drug product test.
- Despite those deficiencies and constraints, all current Lab staff is very enthusiastic and put forth every effort to be ready to performing their functions. [Note: a follow-up communication between USP DQI and the LNCQD indicated that some of the recommendations put forward by the Assessment Team already have been implemented by the Lab, e.g. becoming familiar with simple testing procedures using pharmacopeial monographs to perform tests and assays of some simple drug products.]

5.3. Inspection services

Inspection service in Madagascar was started in 1998, soon after the creation of AMM, when eleven pharmacists were trained by a French Pharmacist-Inspector collaborating with the MOH, French Cooperation, and WHO. Currently four trained inspectors work for AMM but in separate divisions; only one pharmacist-inspector works in the Inspection Division. Until 2003, only the distribution channels were inpected. [Note: Of the eleven inspectors trained, seven currently work for the private sector.]

Inspection service is also in its infancy. Because there are not enough inspectors, budget constraints, lack of transportation, and socio-political events in 2002, only a very limited number of inspections have taken place since 2000. For instance, in 2003 only 12.8% (26 out of 203 pharmacies in the country) were inspected and none of the small retail-drug outlets or manufacturing plants were inspected for GMP compliance. Often, division Chiefs of other divisions (e.g., Registration, and Service for Pharmacy and Medicines of Direction des Pharmacies and Laboratoires) were asked to join and perform inspections. In certain cases, AMM hired private pharmacists (trained in 1998) to carry out inspections. During the 2000-2002 inspections some major findings included inappropriate documentation and poor practice in drug management, e.g. inadequate storage conditions, incorrect labeling, and existence of expiry medicines on shelves. Between 2000-2002, a total of nine sanctions and measures were taken by the National Board of Pharmacists of Madagascar starting from notice of warning to definite closure.

Table 10: Number of pharmaceutical establishments inspected by year.

Establishment	2000	2001	2002
Wholesaler/importer	1 (out of 27) 3.7%	3 (out of 26) 11.5%	5 (out of 24) 20.8%
Pharmacies	19 (out of 205) 9.3%	41 (out of 203) 20.2%	26 (out of 203) 12.8%
Small retail-drug outlets	Data not available	Data not available	None (out of 1625) 0%

Source: AMM, 2003. Activity Report (Rapport d'Activités) 1999-2002

Key findings concerning inspection services of AMM:

- Inadequate human resources.
- Need for training in GMP inspection, sampling procedure and inspection procedure.
- Lack of national GMP guidelines as well as inspection guidelines, e.g. what documents are required and how to verify documentation (although some SOPs on inspection activities exist. Currently European GMP guidelines are accepted for use in the country.
- Lack of import inspection and taking samples for testing.
- Need for elaboration in legislation/regulation concerning inspection, for example, the inclusion of a text stating that all imported (including donated) drugs are subject to inspection and quality testing at the port of entry as well as distribution chain at any time at the discretion of the inspectors.

5.4. Pharmacovigilance (post-marketing surveillance)

The basic function of the post-marketing surveillance division of AMM is to gather and disseminate information on adverse and/or unpredictable reactions of medicines. In 2000, a Pharmacovigilance booklet entitled "Synthesis of articles appeared in the *Revue Prescrire* on adverse drug reactions in Madagascar" was published based on studies done in Madagascar between 1977 and 1997).[11] It also disseminated different warnings and alerts on medicines issued by WHO and other sources.

Key findings concerning Pharmacovigilance Service:

- Limited number of human resources – (currently only one medical doctor is responsible for the service).
- Need for training – how and what is needed for this service;

Lack of capacity in coordinating pharmacovigilance studies which some of the key donors in the country want to carry out on certain products newly introduced, e.g., Palustop and Cura-7 introduced by Population

5.5. Licensing of persons and pharmaceutical establishments

The AMM is not mandated to issue or control the licensing of persons or pharmaceutical establishments. The Service for Pharmacy and Medicines (SPM) of Direction des Pharmacies and Laboratoires (DPL) is responsible for ensuring access to medicines, medical devices, and blood products for health facilities. Besides authorizing and suspending licenses for pharmaceutical establishments, including pharmacies and other retails outlets, based on notice of the appropriate Committee and by order of the AMM, the SPM also:

- Controls, documents, and approves the importation of narcotics and psychotropic drugs;
- Receives and distributes drug donations; and
- Revises and implements national policy on pharmaceuticals (by 2004).

Persons intending to operate any pharmaceutical establishments, a pharmacy for example, must submit an application and meet the applicable criteria and conditions. Once a license is issued, SPM considers its renewal, suspension, and/or revocation based on the report from the AMM Inspectors. Again, only a limited number of inspections have been done since AMM's creation and, so far, only nine sanction cases have been reported in the past three years.

Key findings concerning licensing service:

- This service has limited qualified human resources and limited expertise or experience in drug management and quality assurance.
- Need training in drug management and quality assurance and has asked USP DQI to put them in touch with an organizations that can conduct a training course in drug management and quality assurance. USP DQI will contact MSH/RPM Plus Program on this regard.

5.6. Quality assurance and local drug production

Quality assurance within the local drug production industry has relied on the technical, human, and financial capacity of individual companies, which varies among manufacturers. Currently, three moderate-scale manufacturers (one government (OFAFA) and two run privately (FARMAD and UPROSOL)) operate. The value of the average annual production (ex-factory price) was estimated at US$ 4.11 million. Until 2003, these manufacturers claimed that there had been no mechanism of government support to improve the quality of their products. To gain some perspective, the Assessment Team visited OFAFA; their visit is summarized in Box 1.

Box 1: Case visit to the government-operated manufacturing site, OFAFA

Until 1991, the Chinese Government supported the company. It manufactures some essential medicines, solid (e.g., paracetamol, amoxicillin, chloroquine, and metronidazole tablets) and liquid (e.g., eugenol and metoclopamide solutions, and chloroquine and paracetamol syrups) forms of drug preparations. Apparently OFAFA lacks financial support from the government which makes operating very difficult. The plant is inadequate for drug manufacturing; an urgent renovation of both the building and equipment is needed. The aeration system does not work, many windows are broken, and the environment is not controlled at any level. All the pressing machines are very old, including tableting, granulating, mixing, and other machinery. While they possess basic lab equipment and instruments, those too will require upgrading to improve working conditions. In sum, OFAFA urgently needs new manufacturing and processing machines, new lab equipment, and a new facility in order to become competitive in the marketplace. A huge capital investment would be required to enable to the company to produce high quality standard products.

Due to time constraints, the Assessment Team did not visit the FARMAD plant. FARMAD now imports drugs from outside rather than producing drugs locally; it is cheaper to import because of the high taxes on APIs and excipients.

6. Potential Cooperation and Local Support AMM Could Obtain

There are several potential national and international players in the Madagascar pharmaceutical sector with which the AMM should establish regular communications and contact for assistance in the effort to improve the QA/QC system of the country:

- WHO – a key supporter in QA/QC establishment in this country. It welcomed the collaborative approach initiated by USP DQI and is willing to provide support for both the QA/QC training and technical assistance and in the area of national medicinal drug policy implementation. The AMM and the MOH should submit a formal request to the WHO Representative.

- Institut Malgach des Recherches Appliquées (IMRA) - a private research center whose mission is contributing to the improvement of the medical and social state of the Malagasy people in their natural environment. The IMRA Lab is relatively well equipped with modern instruments and equipment, for example, gas chromatography, HPLC, and infrared spectrophotometer. It carries out different tests and assays, including method and process validation, active ingredient identification and content determination, and bioavailability and toxicity studies. IMRA works in collaboration with the University of Antananarivo, the Université Catholique de Louvain of Belgium, and the Laboratoire de Contrôle et des Standardisations of Université de Liège of Belgium. IMRA expressed its willingness to support MOH efforts and cooperate with AMM to establish a well functioning system for drug quality assurance and control. IMRA has the capacity to train AMM staff in physico-chemical methods, such as HPLC, GC, and UV/VIS spectrophotometry. Many of the IMRA staff are professors with an international track record of excellence in science.

7. Summary of Findings, Conclusion, and Recommendations to Improve the QA Program and QC System in Madagascar

The following summarizes the observations and findings drawn from the USP DQI Assessment Team's one-week visit and outlines what areas need to be addressed to strengthen the drug QA/QC system in Madagascar.

7.1. Strengths and constraints of drug QA/QC

Strengths and potential:

- Strong political will of the MOH to support AMM to become fully operational;
- Since its establishment in 1995, although it is a relatively small and new agency with limited resources, AMM has already started to carry out some services, e.g., inspection and registration;
- AMM staff are very enthusiastic and eager to perform their work to make sure that drugs marketed in the country are of good quality;
- Most aspects of drug quality are included in the current "legislation – in the form of Ordonnance/Decree" and regulations (Recueil de textes legislatifs et reglementaires);
- Some (basic) laboratory equipment and instruments have been installed in the lab through the support and cooperation of the European Union and the Government of France.

Constraints and limitations:

- The lack of qualified human resources has affected the technical capacity of AMM as a national agency responsible for QA/QC; most of those already employed require refresher training in their respective areas of work;
- A "horizontal communication gap" seems to exist between the QA/QC regulators and the regulated. For instance, some key procurement agents in the country lack full knowledge of some of the requirements for registration;
- the current "legislation" or Ordonnance affecting drugs is unclear as to which drugs are subject to registration — all drug products, only those locally produced, or only those imported/exported. This regulatory loophole prevents AMM from exercising its power, for instance, to implement a compulsory registration, and should be amended to laws;
- The country does not have a national medicinal drug policy in place;

[Note: The MOH has acknowledged the major finding of the lack of human resources and lack of drug policy and is already working on recruiting new staff for the positions suggested by the Team.]

7.2. Order of priority for needed improvements and strengthening:

- Strengthening AMM Laboratory for Drug Quality Control
  - Human resources and technical skills:
    - Step 1: Increase number of Lab staff (now 1 pharmacist, 1 chemist, 1 technician) to at least 3-5 for 2004 (1 pharmacist, 2 chemists, 2 technicians), and increase to 8-10 by 2005. MOH/AMM should be primarily responsible for this step.

    - Step 2: Organize basic training on laboratory management, documentation, and testing/analysis of most common and simple essential pharmaceutical products. This can be arranged through collaboration among local institutions, e.g., IMRA, FARMAD, and OFAFA.

    - Step 3: Organize advanced training on good laboratory practices and testing methods using more sophisticated techniques in USP monographs. The modules should include dissolution, UV, HPLC, etc. USP DQI can take the lead in organizing this training.

  - Lab equipment:
    - In concert with Steps 2 and 3 above, there is a need to equip the Lab with some critical equipment and supplies, e.g., an analytical balance; auto-sampler and computer with software for HPLC; tablet harness and friability tester; centrifuge; and Karl Fisher titration. MOH may apply to WHO, EU, and others for support.

  - Expected outcomes:
    - By the end of 2004 – the Lab should be capable of testing the quality of most common essential and priority medicines used in the country;
    - By the end of 2005 – the Lab should be in full operation, that is, able to provide solid data and information on the quality of most pharmaceutical products to the

authority and interested parties enforcing the legal and administrative function of AMM in drug quality assurance and control.

- **Product quality assessment and registration**
  - Human resources – Need to add at least one more person to the existing staff of one, either a pharmacologist or medical doctor to evaluate drug from efficacy and safety perspective;
  - Training – in drug dossier evaluation and, perhaps, in "computerized" registration; and
  - Access to wider drug quality, safety, and efficacy information sources.

- **Inspection services:**
  - Human resources – The three existing inspectors address the distribution chain only, not GMP compliance of manufacturers, although some inspection services are subcontracted to private inspectors. Two more inspectors are needed by 2004, or it would be practical to train the provincial health (pharmacy) officer to assist;
  - Training – in GMP inspection and sampling procedure;
  - Import inspection and taking samples for testing – legislation/regulation development; what documents are required and how to verify documentation. Imported drugs, including donated drugs, are subject to inspection and quality testing at the port of entry and along the distribution chain at any time at the discretion of the inspectors.

- **Pharmacovigilance service/post-marketing surveillance**
  - Human resources – at least two additional staff for 2004 (2 pharmacists or pharmacologists), increasing to four or five by 2005;
  - Training – how and what is needed for this service;
  - Coordinate pharmacovigilance studies; and
  - For the long-term, this service should be linked to the creation of a drug information center.

- **Legislation/regulation and national drug policy**
  - Policy development:
    Revise and implement a national drug policy (NDP) – based on WHO's Essential Drug Concept – aimed at ensuring equitable access to high quality medicines to all who need them, and containing the following main components:
    1. Equitable access to essential medicines
    2. Quality assurance of medicines
    3. Rational use of drugs
    4. Viable pharmaceutical industry

    All stakeholders should be involved in the development process: The Ministries of Health (Agence du Medicament, Service de Pharmacies et Laboratoires), Industry, Commerce, Trade, Finance, and Justice departments; consumers; academia; and professional associations.

- Policy implementation:
  The Cabinet of Ministers should approve the NDP document. For effective implementation, the policy should be *enacted into legislation* in order for key (if not all) aspects and practices to be legalized and regulated.

  An example of the preamble or general section of the law stated that "all drugs to be introduced, marketed, and used in Madagascar are subject to registration. These include those that are imported (including donated medicines), and locally produced (including compounding and/or packaging)."

  Clear guidelines for implementation of the policy need to be developed as the NDP is developed, or soon afterwards, and they should be signed by the Prime Ministerial Cabinet. The guidelines should spell out clearly the responsibilities of each agency or stakeholder. A timeline and estimated budget should also be established.

Annex

Information Collection Questionnaire

The questionnaire below serves as a guide to obtain general information and specific data for the review and assessment of a drug quality assurance program and drug quality control system. It is classified into four major categories based on the methodological framework described above.

Note: Every effort has to be made to obtain the most up-to-date data and information. If multi-year data is involved, indicate the year next to the data.

1. Background information, e.g., country information, demographic and socio-economic, health, and pharmaceutical data;
2. Pre-marketing quality assessment;
3. Regulatory functions; and
4. Technical elements.

Background information (Indicate the year the data was collected.)

1. Country information
    a. Area (in sqKM):_____
    b. Administrative divisions (# of provinces, states, districts)_____
    _____

2. Demographic and socio-economic
    a. Total population: _____
    b. Population distribution (urban vs. rural)_____
    c. Life expectancy (male/female)_____
    d. Literacy rate_____
    e. Gross domestic product per capita _____ (year:_____)

3. Health and health system data
    a. Infant mortality rate (per 1000 live births) _____
    b. Maternal mortality rate (per 100,000) _____
    c. Total government health expenditure _____
    d. Total value of international aid for health sector _____
    e. Total number of health facilities both public and private (provide data in Table below) – indicate the year the data applied _____

Health Facilities	Government/Public	Private
Central		
Provincial/State		
District		
Health Center		

4. Pharmaceutical sector data - indicate the year the data applied _____

a. Total government pharmaceutical expenditure _____
b. Per capita drug expenditure _____
c. Total value of domestic pharmaceutical production _____
d. Total value of imports of finished drug products _____
e. Total value of imports of APIs _____
f. Total value of exports of finished drug products _____
g. Total value of exports of APIs _____

5. Country health and pharmaceutical human resources

Description		Year
Type and number of health professional training schools		
	Medical	
	Pharmacy	
	Others, e.g., dentistry, nursing	
Number of health professionals		
	Total number of medical doctors	
	Total number of pharmacists	

6. Country pharmaceutical sector status (specify year)

No. of establishments		Government	Private	Others	Year
Pharmaceutical manufacturing plants					
	For APIs				
	For finished dosage forms				
	For packaging finished dosage forms				
Research-based pharmaceutical industry					
Generic (incl. branded) pharmaceutical product manufacturers					
Pharmaceutical importers					
Pharmaceutical wholesalers					

7. Evolution of drug regulation
   a. The year when the drug law or regulation was first introduced _____
   b. The title of the first law/act/regulation enacted _____
      _____

   c. Which of the following aspects of drug quality, safety, efficacy are covered by present drug law(s) or regulations:

- Registration – Yes_____ No_____
- Drug product licensing – Yes_____ No_____
- Pharmaceutical establishment licensing – Yes_____ No_____
- Control of drug importation – Yes_____ No_____
- Control of drug exportation – Yes_____ No_____
- Inspection services – Yes_____ No_____
- Monitoring for quality and ADR – Yes_____ No_____
- Control of drug promotion and advertising – Yes_____ No_____
- Drug quality testing/control – Yes_____ No_____
- Control of clinical trials – Yes_____ No_____
- Others (specify) – _____

d. Existence of national drug regulatory agency: Yes_____ No_____
If yes, describe its key functions:

- _____
- _____
- _____
- _____
- _____
- _____

Pre-marketing quality assessment (licensing and registration)

1. Existence of drug product assessment unit/team – Yes_____ No_____

2. Is there a specific budget for licensing and registration –Yes_____ No_____
If yes, please specify sources: Government _____(year: _____)
Fees _____(year: _____)

3. How many licenses have been issued, renewed, suspended, or revoked in the last three years?

Action	Year:	Year:	Year:
New licenses issued			
Renewed			
Suspended			
Revoked			
Other (specify)			

4. Are there unlicensed or illegal establishments engaged in the manufacture, import, export, or retail sale of pharmaceutical products in the country?

If Yes to any of the above, provide estimated number in Table below

Type of establishment engaged in	Year:	Year:
Manufacture		

Import/export		
Wholesale		
Retail sale		

5. Does the country allow the import of unregistered pharmaceutical products?

   Yes_____ No_____
   If yes, please briefly explain as in what circumstances, e.g., donated medicines or emergency.
   _____

6. What key professional qualifications are required to obtain a license to engage in or operate the following pharmaceutical activities?

Practice/activity	**Professional requirement**
Manufacturing	
Importing/exporting	
Wholesaling	
Retail selling/pharmacy	

7. Is GMP compliance and inspection of the manufacturing site a pre-condition for licensing of a manufacturing plant?
   Yes_____ No_____

8. Key technical requirements for drug registration:
   a. Product quality, safety, and efficacy data – Yes_____ No_____
   b. Interchangeability data (e.g., BE) for generic – Yes_____ No_____
   c. Clinical trials data – Yes_____ No_____
   d. Registration in other countries – Yes_____ No_____

9. Are the same requirements applied to both innovator (branded) products as well as generics?
   Yes _____ No _____ If No, what requirements are different:
   _____

10. Pharmaceutical product assessment (for registration) capability:
    a. Maximum number of pharmaceutical products assessed per year _____
    b. Number of actual pharmaceutical products assessed in
       i. Year, e.g., 2001 _____
       ii. Year, e.g., 2002 _____
       iii. Year, e.g., 2003 _____

11. Pharmaceutical product registration:
    a. Number of pharmaceutical products/preparations officially registered in the country _____ (Year_____) of which
    b. Generic (including branded generic)_____

12. Registration validation is for: a. 2 years _____
    b. 3 years _____

c. 4 years _____
d. 5 years _____
e. > 5 years _____

13. Average fees/costs for a drug registration: _____(USD)

14. Lead time (i.e., the time span between application submission and the date of issuance of the license) taken for registering a pharmaceutical product.
_____

15. Existence of fast-track registration system: Yes_____No_____
If yes, indicate conditions for a product to be eligible for fast-track registration:
_____
_____
_____

16. Are guidelines/instructions on drug registration available and freely accessible:
    a. On the internet or web _____
    b. In hard copies _____

17. Current registration system:
    a. Manual _____
    b. Computer-assisted _____

Regulatory functions

(Cover central administration – allowing the functioning of regulatory authority, quality control, inspection services, control of pharmaceutical promotion, advertising, and recall).

A. Central administration

1. Existence of a central administration office that oversees key pharmaceutical activities and functions (product assessment, licensing of persons, premises, and practices, registration, inspection, and post-marketing surveillance):
Yes_____ No_____
If yes, name it_____
_____

2. Professional qualification and the number of people working at central administration – provide year when data/information is obtained _____

Qualification	Pharmacy/ pharmaceutical sciences	Medical Sciences	Other
Post-graduates			

Graduates			
Technicians			
Other (specify)			

3. Professional qualifications and the number of people working in the following functions – provide year when data/information is obtained _____

Function	Post-graduates	Graduates	Other (specify)
Drug product assessment			
Licensing			
Registration			
Inspection			
Post-marketing			
Other (specify)			

B. Laboratory control/testing:

1. Existence of a national drug quality control lab (NDQCL)
   Yes_____ No_____
   If yes, obtain the following data and information

2. Number of units/divisions of the Lab and name of each unit/division:
   No. of units/divisions: _____
   Name of each unit/division: _____
   _____
   _____
   _____
   _____
   _____
   _____

3. Professional qualification and the number of people working at NDQCL – provide year when data/information is obtained _____

Qualification	Pharmacy/ pharmaceutical sciences	Chemistry	Other
Post-graduates			
Graduates			
Technicians			
Other (specify)			

4. What kind of tests or assays the Lab can perform:
   a. Identification Yes_____ No_____
   b. Hardness (for solid form) Yes_____ No_____

c. Loss on drying Yes_____ No_____
d. Melting range Yes_____ No_____
e. Residue on ignition Yes_____ No_____
f. Disintegration Yes_____ No_____
g. Dissolution Yes_____ No_____
h. Assay for content of API(s) Yes_____ No_____
i. Any of the following special tests:
   - Sterility Yes_____ No_____
   - Pyrogen Yes_____ No_____
   - Bacterial endotoxin Yes_____ No_____
   - Biovailability Yes_____ No_____
   - Bioequivalence Yes_____ No_____
   - Other (specifiy)_____

5. The Lab is capable of conducting the test for:
   a. Impurities (ordinary impurities) Yes_____ No_____
   b. Water content Yes_____ No_____
   c. Heavy metals Yes_____ No_____

6. Existence of a national pharmacopeia: Yes_____ No_____
   If yes, provide name, year first published, and current edition
   _____

7. Name of pharmacopeias officially accepted for use in the country:
   - _____
   - _____
   - _____
   - _____
   - _____
   - _____

8. Functioning lab equipment and instruments: Specify in the table below all equipment and instruments the Lab possesses and provide the information required:

Description of equipment/instrument	Model/type	Quantity	Year introduced	Functioning status
e.g. dissolution tester	Pharma Test PTZ1E	1	1996	Working - requires calibrating

9. Estimated maximum number of samples (including APIs and finished products) the Lab is able to test per year _____

10. Tests (with results) that were performed by the Lab in the current and last three years:

Total No. of samples tested	No. passed quality testing	No. failed quality testing
APIs		
Year:		
Year:		
Year:		
Year:		
Finished drug products		
Year:		
Year:		
Year:		
Year:		

11. Specify the most common drug groups (e.g., antibiotic, antipyretic, anti- inflammatory, etc.) that the Lab has tested.
    - _____
    - _____
    - _____
    - _____
    - _____

12. Sites that have sent drug samples or APIs and requests for tests:
    - e.g., inspection unit of Department of Food and Drugs
    - _____
    - _____
    - _____
    - _____

13. Purposes for quality testing of drug samples in the last two years:

Purpose	No. and year:	No. and year:
Registration		
Quality monitoring		

Manufacturing (in process control)		
Request from drug industry		
Request from individuals		
Administrative or regulatory action		
Other (specify)		

14. Does the Lab charge fees for testing services? Yes_____ No_____
    If yes, indicate the average charge per sample testing _____ USD

15. Total annual budget for the Lab operation including salaries of staff
    _____ USD (year_____)

16. Total annual budget for the Lab equipment/instrument maintenance
    _____ USD (year_____)

17. Major sources of budget for the Lab operations/activities, specify:
    _____
    _____

18. Has the Lab received any technical or financial support (or in-kind) from any international agencies since its establishment?
    If yes, indicate estimated value or type of equipment and year of support:
    - _____ year_____
    - _____ year_____
    - _____ year_____
    - _____ year_____
    - _____ year_____

19. Main constraints faced in conducting the various tests/assays in the Lab. *Circle* all answers that apply:
    a. Financial constraints – low government budget
    b. Limited numbers of qualified professionals
    c. Lack of continuing education/training
    d. Limited number of adequate lab equipment/instrument
    e. Unavailability of certain reference standards/substances
    f. Unavailability of pharmacopeial specifications
    g. Unavailability of certain reagents, solvents, and indicators.
    h. Other (specify) _____
       _____
       _____

20. Lab management vis-à-vis Good Laboratory Practice. *Circle* all answers that apply:
    a. Existence and use of sample receiving/collection note book
    b. Existence and use of laboratory note book
    c. Existence and use of analytical work book or work sheet

d. Existence and use of lab equipment log book
e. Existence (in written document) of safety rules and measures applied
f. Existence and use of appropriate lab clothes, gloves, goggles, etc.
g. Existence and use of appropriate and separate storage room for reference substances, toxic and poison, and inflammable chemicals.
h. Working reagents, references, solutions, solvents, and samples are appropriately labeled (at least their name, concentration, date of preparation, initial of preparatory, multiplication factor- as necessary)
i. Existence and use of standard operating procedures for testing
j. Existence and use of air-sucking chamber
k. Other _____

21. Has the Lab participated in any international or regional assessment for professional and technical competency? If yes, describe the event and the year:
_____
_____

22. Has the Lab ever been requested to test a certain product's quality by an international agency or neighboring countries? If yes, describe the event and the year:
_____
_____

23. Has the Lab received any complaints regarding its testing results in the past three years? If yes, briefly describe the event: _____
_____

C. Inspection services

1. Existence of provisions in the drug law/regulations defining the powers and status of GMP inspectors: Yes _____ No _____

2. Existence of a GMP inspectorate: Yes _____No _____
If yes, provide number of inspectors and indicate whether they also serve as inspectors for drug supply chain: Yes _____No _____

If no, indicate whether inspection services are subcontracted:
Yes _____ No _____

3. Relationship of GMP inspectorate to the unit/division in charge of licensing of manufacturers and product registration unit/division:
_____
_____

4. Existence of national GMP guidelines: Yes_____ No_____
If yes, give its name and year of introduction _____
_____ (year_____)
If no, what GMP guidelines are officially accepted for use in the country?

_____

5. Existence of manuals or standard operating procedures (SOPs) for GMP inspectors:
   Yes_____ No_____
   If yes, provide name and date of publication: _____
   _____(year_____)

6. Status of application of GMP guidelines/standards for manufacturing plants:
   Voluntary _____ Compulsory (required by law) _____

7. Information on current GMP inspection-related activities:

No. of plants and type of inspection	Year:	Year:	Year:
Total No. of manufacturing plants in the country			
No. of plants inspected and compliant to GMP			
No. of plants inspected for renewal of license			
No. of plants inspected because of complaints			
No. of plants inspected as follow-up			
Other (specify)			

8. Number of administrative or regulatory measures taken against GMP non-compliant manufacturing plants in the last three years:

Measures taken:	Year:	Year:	Year:
Written notice of warning			
Fines			
License suspended			
License revoked			
Production suspended			
Other (specify)			

9. Plan to increase number of manufacturing plants to comply with GMP standards:
   Yes _____ No _____
   If yes, indicate target number by year

Target to increase GMP compliance:	Current year:	Year:	Year:
No. of GMP non-compliant manufacturing plants			
No. of GMP compliant plants			

10. Inspections in the drug supply/distribution chain – existence of inspection services in the drug supply chain: Yes _____No _____
    If yes, indicate number of inspections per year planned: _____

11. Are samples collected during inspections? Yes _____ No _____
    If yes, provide information below:

Samples collected and tested in connection with:	No. of samples collected	Passed quality testing	Failed quality testing

	Year:		Year:		Year:	
GMP inspection						
Supply chain inspection						
Other (specify)						
Total						

12. Number of administrative and/or regulatory measures taken against practices related to producing and/or selling poor quality products in the last three years:

Measures taken:	Year:	Year:	Year:
Written notice of warning to manufacturer, wholesaler, and retailer			
Fines			
License suspended			
License revoked			
Product recall			
Product withdrawal			
Other (specify)			

13. Does the inspectorate charge fees for inspection services?
    Yes _____ No _____
    If yes, indicate rough fees charge per inspection: _____ USD

14. Existence of mechanism or system for monitoring of quality of medicines as post-marketing surveillance activity: Yes _____ No _____
    If yes, briefly describe the mechanism _____
    _____
    _____
    _____

15. Existence of product quality and adverse drug reactions reporting mechanism or system: Yes _____ No _____
    If yes, briefly describe the mechanism _____
    _____
    _____
    _____

16. Existence of product recall mechanism or system: Yes _____ No _____
    If yes, briefly describe the mechanism _____
    _____
    _____
    _____
    _____

17. Main constraints faced in carrying out inspection services. *Circle* all answers that apply:
    a. Financial constraints – low government budget
    b. Limited numbers of qualified inspectors

c. Lack of continuing education/training
d. Lack of SOP or guidelines
e. Limited access to relevant information on inspection
f. Other (specify) _____
_____
_____

Technical elements and post-marketing surveillance

Technical elements and post-marketing surveillance have been incorporated into the previous three sections.

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Attachment 1

PROGRAMME EFFECTIF – MISSION U.S. PHARMACOPEIA – 13 Octobre au 17 Octobre 2003

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Date	Heures	Activités	Lieux	Personne-contact	Invités
Lundi 13 Octobre 2003	07 h 00	- Entretien du Dr Souly Phanouvong et du Dr Abdelkrim Smine avec l'équipe de l'USAID	Hôtel Colbert	Dr Noé Rakotondrajaona	
	09h 00	- Visite de courtoisie à Monsieur le Ministre de la Santé	Ministère de la Santé	Directeur de cabinet/SG	Les experts seront accompagnés par l'Equipe de USAID
	10 h 00	- Présentation de l'Agence du Médicament : les différents services (inspection, enregistrement, pharmacovigilance, contrôle de qualité), le laboratoire de contrôle de qualité - Présentation de la DPL : Organigramme de la Direction des Pharmacies et Laboratoires et des activités du SPM : Service des Pharmacies et Médicaments	Salle de réunion de l'Agence du Médicament	Dr. Jean René Randriasamimanana Dr Clara Rajemiarimoelisoa	
	12h 30	- Déjeuner			
	14 h 30	- Etat des lieux du laboratoire de contrôle de l'Agence du Médicament - Entretien avec les principaux responsables de l'Agence du Médicament+w : inspection, enregistrement, pharmacovigilance	Agence du Médicament	Mme Hanitra Ravelojaona	

Mardi 14 Octobre 2003	08 h 30	- Entretien avec le Directeur Général de OFAFA	OFAFA	Directeur Général OFAFA	
	12 h 30	- Déjeuner			
	14h 00	- Entretien avec le Task manager de la Banque Mondiale	Siège de la Banque Mondiale	Dr Jean-Pierre Manshande	
	15h 30	- Entretien avec le Directeur général de PSI Madagascar	Siège de PSI	M. David Mac Afee	
	17 h 00	- Entretien avec Madame le Représentant de l'UNICEF	UNICEF	Madame le Représentant de l'UNICEF	
Mercredi 15 octobre 2003	09 H 00	- Entretien avec Monsieur le Représentant de l'OMS	OMS	Monsieur le Représentant de l'OMS	
	10h30	- Entretien avec la Mme la Présidente de IMRA	IMRA	Mme Ratsimamanga	
	12h30	- Déjeuner			
Date	**Heures**	**Activités**	**Lieux**	**Personne-contact**	**Invités**
Mercredi 15 octobre 2003	14h 30	- Entretien avec le Directeur Général de FARMAD	FARMAD	M. Michel Ramanantsoa	
Jeudi 16 octobre 2003	09 h 00	- Séance de travail avec les bailleurs de fonds sous l'égide de Monsieur le Secrétaire Général du Ministère de la Santé	Salle de conférence du Ministère de la santé	Dr. Jean René Randriasamimanana	Bailleurs :OMS, USAID, Banque Mondiale (CRESAN), Union européenne Autres invités : PSI, DLMT
	11 h 00	- Séance de travail sur les équipements : maintenance, qualification, vérification périodique ….	Salle de réunion de l'Agence du Médicament	Mme Hanitra Ravelojaona	DPL, SPSM, Service des Laboratoires
	12h 00	- Déjeuner			
	14 h 30	- Visite de la Centrale d'Achats Salama	Salama	Dr. Jean René Randriasamimanana	

	16h30	- Etablissement du projet de protocole de collaboration entre le Ministère de la Santé et l'USP par les experts de US Pharmacopeia		Dr. Jean René Randriasamimanana	
Vendredi 17 octobre 2003	9 h 00	- Présentation de l'US Pharmacopeia et de l'US DQI aux différentes entités impliquées dans le secteur pharmaceutique	Ex-Solimotel	Dr. Jean René Randriasamimanana	SAN/CAB, SG, CGP, DAM, DPL, DSF, DG CHU, SPSM, CNARP, IMRA, FARMAD, OFAFA, Salama, Union européenne, IPM, OMS, UNICEF, USAID, UNFPA, CRESAN, ONP, ONM, ONCD, Faculté des Sciences, Faculté de Médecine, Attaché de presse
	12 h 00	- Cocktail	Ex-Solimotel	Dr. Jean René Randriasamimanana	
	14 h 30	- Discussion sur le projet de protocole de collaboration entre le Ministère de la Santé de Madagascar et l'US Pharmacopeia	Salle de conférence du Ministère de la Santé	Dr. Jean René Randriasamimanana	SAN/CAB, SG, DAM, DPL, CGP, DREP, CGP, DG Salama, OMS, USAID, Attaché de presse