Pharmaceutical regulation: A twelve country study

(*A Pharmaceutical Assessment Management and Policy (PAMP) practicum report)*

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Abbreviations

ADR	Adverse Drug Reaction
EMP	Essential Medicines and Pharmaceutical Policy
GCP	Good Clinical Practice
GDP	Good Distribution Guidelines
GMP	Good Manufacturing guidelines
GNI	Gross National Income
HAI	Health Action International
INN	International Non-Proprietary Name
MA	Marketing Authorization
MOH	Ministry of Health
MRA/DRA	Medicines Regulatory Authority/Drugs Regulatory Agency
NCE	New Chemical Entity
NMP	National Medicines Policy
SPC	Summary Product Characteristics
TPE	Total Pharmaceutical Expenditure
WHA	World Health Assembly
WHO	World Health Organization

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Executive Summary

This report presents the results and analyses of the regulatory section of a survey on the pharmaceutical sector profiles of 12 countries (Argentina, Armenia, Austria, China, Jordan, Kenya, Maldives, Nigeria, Pakistan, Sri Lanka, Sudan and Suriname). The report was compiled by Paul Ashigbie a Master of Public Health student from Boston University for the World Health Organization (WHO). Dr Richard Laing, the leader of Medicine Information and Evidence for policy team of the Essentials Medicines and Pharmaceutical Policy (EMP) department of the WHO supervised the compilation.

The objective of the 2010 pilot study was to develop model pharmaceutical country profiles. The pilot study precedes a bigger study that will involve all of WHO member states in 2011. Since the World Health Assembly (WHA) passed a resolution in 1975 calling on the WHO to be of greater direct assistance to member states in implementing national programs on pharmaceutical regulation and the formulation of national drug policies, the WHO have undertaken a number of studies to assess the pharmaceutical situation in its member states. These studies included the 1999 World Medicine Situation which was published in 2004, the 2003 levels I and II surveys, the 2007 level I survey, the 2002 ten country study on effective drug regulation, the pharmaceutical regulatory assessments in some member states of the WHO, and the 2010 country profile pilot study of which the regulatory section is the focus of this report.

Method

Data for this report was obtained by three main methods. The first method involved reviewing the answers provided by the countries on the 2010 pharmaceutical country profile pilot study instrument. The second method involved reviewing the other supporting documents added to the survey results. For example, regulatory legislations, code of conducts, standard operating procedures (SOPs), adverse drug reaction (ADR) reports etc. submitted by the study countries, to confirm information already provided on the survey instrument or look for a new information altogether. The third method involved by browsing the websites of the Medicines Regulatory Authorities (MRAs) and other relevant websites for information.

Findings

The findings of the survey are summarised under the major regulatory functions and structure below:

Profile of the study countries: The study countries were purposively selected to provide different country situations. Therefore these countries varied widely in terms of socio economic indicators such as population density, gross national income (GNI) per capita, average life expectancy and under five mortality rate. The countries also differed in their pharmaceutical sector indicators such as total pharmaceutical expenditure, number of licensed pharmacies, number of licensed manufacturers and the number of registered products. The aim of selecting countries with different backgrounds was to obtain countries with different situations and not to obtain a sample representative of all member countries of the WHO.

Regulatory framework and capacity: All of the 12 countries had legal provisions establishing the powers and responsibilities of their MRAs. However, only seven reported assessing their regulatory system within five years prior to the study. Regular assessment of regulatory systems is important in making the necessary adjustments to cope with the rapidly changing regulatory demands in the pharmaceutical sector. Nine of the 12 MRAs had their own websites. This is encouraging considering the fact that in the 2003 level I and II survey, less than half (51 out of 136) MRAs had their own websites.

All of the MRAs received funds from the regular budget of their governments except in Kenya and Armenia. Seven MRAs (in Argentina, Armenia, Austria, Jordan, Kenya, Nigeria and Sudan) were partially funded from fees for services. Eight MRAs received funding from other sources. China was the only country that relied solely on government funding which could make the MRA of the country free from regulatory provider capture but not free from governmental control.

Marketing authorization (MA): All of the twelve countries had legal provisions requiring marketing authorization of all pharmaceutical products, legal provisions requiring for the registration of medicines by INN name or Brand name with INN name, as well as a publicly available criteria for assessing applications for marketing authorization. However, legal provisions for publishing the list of registered pharmaceutical products did not exist in Kenya, Sri-Lanka and Jordan. In addition legal provisions requiring the publication of Summary Product Characteristics (SPC) of registered medicines was the least available in the study countries (5 out of 11 respondents). Furthermore, legal provisions requiring the declaration of potential conflict of interest for experts involved in

the assessment and decision making during drug registration, a good indicator of transparency, was also less common in the study countries (six out of eleven respondents indicated having this provisions).

The ratio of the fee of registering a New Chemical Entity (NCE) to that of a generic ranged from 1 to 9. On average the fees for registering NCEs was three times higher than the fees for registering generic products. This ratio does not indicate significant promotion of generic pharmaceuticals through MA application fees.

Inspection: All of the 12 countries had legal provisions permitting inspectors to inspect premises as well as provisions making inspection a pre-requisite for licensing of facilities. The ratio of the number of inspectors to 100 pharmacies was highest in Nigeria, which is relatively favorable to effective inspection compared to the lowest ratio of 0.1 per 100 in Sri-Lanka.

Import control: All of the eleven respondent countries had legal provisions requiring authorization before importing medicines as well as legal provisions requiring the sampling of imported products for testing. In general, legal provisions on import control existed in all the respondent countries. The widespread existence of legal provisions on import control was also observed in the 2002 ten country study, in conformity to the WHO guidelines on importation of pharmaceutical products.

Licensing: All of the 12 study countries had legal provisions requiring manufacturers and distributors to be licensed. Compared to the existence of legal provisions requiring compliance with Good Manufacturing Practice (GMP) which existed in eleven countries, legal provisions requiring compliance with Good Distribution Practice (GDP) was less common (existed in only half of the study countries). The 2002 ten country study also concluded that the regulation of manufacturing receives more resources and attention than the regulation of distribution. The publication of GMP and GDP requirements was done in only about a half of the study countries. Apart from improving transparency in the licensing of premises, the publication of GMP and GDP requirements will also facilitate the implementation of these requirements.

Market control and quality control: Out of 11 respondent countries, ten reported having legal provisions controlling the pharmaceutical market. Market control is very important in the pharmaceutical sector to prevent market failure because of the high level of asymmetry in information among the stakeholders involved. It is worth noting that similar to the results of the 2002 ten country study, all of the countries in the 2010 pilot study had a quality control laboratory and did not contract quality control services from

other countries. Inspectors in all of the 12 pilot countries also collected samples for post marketing surveillance testing. However, only Austria and China claimed to make quality testing results publicly available. This also shows a low level of transparency.

Advertisement and promotion: All of the countries had legal provisions to control the promotion and advertising of prescription medicines. This together with the 2002 World Medicines Situation report and the 2003 levels I and II survey indicates a wide presence of legal provisions on the control of advertisement and promotion in countries over the years. All the study countries except Armenia, Sri Lanka, Sudan and Suriname had national codes of conducts on advertisement and promotion. Only China and Nigeria out of the five countries with formal processes for handling complaints and sanctions, claimed to have made public the list of complaints and sanctions that took place 2 years prior to the study. This level of transparency was missing in the other countries.

Clinical Trials: Maldives did not respond to any of the questions on Clinical Trial regulation because clinical trials were not permitted in the country. Sri Lanka was in the process of drafting its legislations on clinical trials at the time of the study. The remaining ten countries had legal provisions requiring MRA's authorization for conducting clinical trials as well as legal provisions requiring authorization by an ethics committee or institutional review board of the clinical trials to be performed. Only Austria, China, Nigeria and Pakistan had legal provisions that required compliance of the manufacturing of investigational products with GMP. While Austria, China, Jordan, Kenya, Nigeria and Pakistan had legal provisions that required compliance with Good Clinical Practice (GCP), only four of these countries (Austria, China, Nigeria and Pakistan) published these GCP regulations, indicating inadequate transparency. The publication of GCP regulations is also likely to encourage compliance from all the stakeholders.

Controlled substances: All of the study countries were signatories to the four international conventions on narcotic drugs. Though the twelve countries had national laws on the control of narcotics, only four (Armenia, Pakistan, Sri-Lanka and Suriname) have had their regulations reviewed by a WHO International Expert or Partner Organization to assess the balance between the prevention of abuse and access for medical need. However this review is necessary to improve access to controlled medicines as the WHO has identified the lack of access to medicines controlled by international treaties.

Pharmacovigilance: Legal provisions for pharmacovigilance activities existed in only five out of nine respondent countries. The other strengths in pharmacovigilance in the countries included the following: Ten out of 11 countries had pharmacovigilance centers

linked to MRA and the use of official standard forms for reporting ADRs in all 11 respondent countries. The shortfalls that were identified included the publication of ADR bulletin in only 6 out of 11 countries and the few countries which used local pharmacovigilance data in making regulatory decisions 2 years prior to the study (3 out of 8 countries). Compared to health workers, consumers less frequently reported ADRs in the study countries.

Conclusions

Based on the results of the 2010 pilot study, the following conclusions could be drawn on the pharmaceutical regulatory systems of the study countries:

i) Generally, legal provisions exist that establish the regulatory framework of MRAs in the study countries. Legal provisions on marketing authorization, regulatory inspection, import control, licensing, market control and quality control, medicines advertising and promotion, and controlled substances were common and comprehensive in all of the study countries.

ii) Legal provisions regulating clinical trials and pharmacovigilance were less common in the pilot countries.

iii) Assessments of national regulatory systems within five years prior to the study were undertaken in only seven out of the ten countries.

iv) Out of the twelve countries, eight regulatory agencies were funded by government budgets, seven by fees from user services and eight by funds from other sources which were mainly donors. None of the countries were funded by user fees alone and China was the only country in which the MRA relied solely on the government budget.

v) More MRAs now have their own websites.

vi) Legal requirements that MRAs be transparent in the execution of their mandate were less common. Examples of these provisions include: Legal provisions requiring the declaration of potential conflict of interest for experts involved in the assessment and decision making for registration and the publication of summary product characteristics of registered medicines. Furthermore, the publication of a list of different categories of pharmaceutical facilities and products, the publication of quality testing results, the publication of GMP, GDP and GCP requirements and the publication of the list of complaints and sanctions concerning violation of codes of conducts were rarely done in the countries.

vii) The application fee for the registration of New Chemical Entities and the registration of generic products were the same in three countries, while the former was higher in five other countries. The average ratio of the registration fee for NCE to generic of 3 appears to be too low and does not reflect the promotion of generic products.

viii) Legal provisions on Good Manufacturing Practice were more comprehensive and

more common than legal provisions on Good Distribution Practice in the countries.
ix) Though pharmacovigilance activities widely existed in the study countries, legal provisions backing these activities were less common.
x) Compared to health care professionals, consumers less frequently reported ADRs in the study countries.

Recommendations

The following recommendations are offered in order to improve the 2011 global pharmaceutical profile study.
i) Soliciting for the total number of licensed pharmacies (as in section 2.02.10) alone may not give a true picture of the pharmaceutical care providers in the study countries. Apart from licensed pharmacies, licensed chemical stores, or other similar facilities which are also regulated exist in some countries. Knowing the number of these facilities will give a good indication of the total number of pharmaceutical care providers in the countries.
ii) The definition for 'inspectors' in section 4.03.02.01 could be more specific and should not include regulatory staffs who work in the laboratory or staff that perform other regulatory duties apart from inspection.
iii) The current definitions for an MRA being part of the MOH or semi-autonomous could make an MRA classifiable into both groups, as could be seen from the study results. The definitions of these two groups should therefore be streamlined.
iv) Section 4.07.06.01 aims to find out whether the code of conducts on advertising and promotion applies to domestic manufacturers, multinational manufacturers or both. Pharmaceutical wholesalers could also be listed as one of institutions to which the code of conduct could apply. Also, the possible answers provided for this section on the survey instrument should be the list of these institutions rather than a ‘yes’ or ‘no’ option.
v) The time limit for the registration of products sought in section 4.02.16 could further be clarified in terms of whether it is the actual time it takes to register a product or whether it is the supposed time. The time it takes to register an NCE and a generic could also be separately evaluated.
vi) Apart from the investigation of legal provisions for promotion of advertisement of pharmaceutical products, the existence of legal provisions regulating the promotion and advertisement of pharmaceutical premises (pharmacies and licensed chemical shops) could also be investigated.

1. Introduction

This report presents the results and analyses of the regulatory section of a survey on the pharmaceutical sector profiles of 12 countries (Argentina, Armenia, Austria, China, Jordan, Kenya, Maldives, Nigeria, Pakistan, Sri Lanka, Sudan and Suriname). This was compiled by Paul Ashigbie a Master of Public Health student from Boston University for the World Health Organization (WHO). The compilation was supervised by Dr Richard Laing, the leader of Medicine Information and Evidence for policy team of the Essentials Medicines and Pharmaceutical Policy (EMP) department of the WHO.

The pharmaceutical sector profile survey was carried out by the country groups with support from the EMP department of the WHO between June and July 2010 as a pilot study to develop model pharmaceutical sector country profiles. It is a continuation of efforts by WHO to regularly assess and help develop pharmaceutical systems of member countries since the World Health Assembly passed a resolution on therapeutic and prophylactic substances in 1975 (1-5). The resolution called on the WHO to be of greater direct assistance to member states in implementing national programs on regulatory control, management and monitoring of drugs, and in the formulation of national drug policies (1). This led to the publication of the first World Drug Situation in 1988 (3). To trace the development of pharmaceutical regulatory profiles of member states over the past decade, the background section of this report chronicles a summary of major studies by the WHO on country regulatory systems of its member countries from 1999 to 2010 (6-9).

This report focuses only on the regulatory section of the pilot study which had seven other sections (10). Apart from the information from the regulation section of the country profile survey, data for this report was also obtained from other documents such as regulatory legislations and code of conducts, standard operating procedures, adverse drug reaction reports, etc submitted by the study countries as well as information from the websites of the regulatory authorities and other relevant websites (see Annex 1 for the list of websites searched).

The results section of the report first summarizes the profile of the 12 countries and the general outcomes of the 2010 country profile study. This is followed be a detailed presentation of the results of the regulatory section of the survey under the following regulatory areas: regulatory framework and capacity, marketing authorization, regulatory inspection, import control, licensing, market and quality control, of drug advertisement and promotion, clinical trials, controlled medicines, and pharmacovigilance. This report also discusses the results of the 2010 survey and 2002 study of effective drug regulation

and compares the 2010 survey results with relevant data from 1999, 2003 and 2007 WHO levels I and II country surveys (6-9).

2. Background

The 20th World Health Assembly (WHA) in 1975 passed a resolution calling on the WHO to help member states formulate national medicines policies, and provide direct assistance to member states on regulatory control, management and monitoring of drugs among others (1). This resolution resulted in the publication of the first World Drug (Medicine) Situation report in 1988 (2).

To be of direct assistance to member states in regulating medicines, the WHO has set up an initiative under its Technical Cooperation on Essential Drugs and Traditional Medicine program to assess the regulatory systems and build the skills and capacity of member states (11). By providing guidance and support for efficient medicines regulatory systems, the WHO aims to develop internationally recognized norms, standards and guidelines, as well as enable countries to implement global guidelines to meet their specific medicines regulatory environment and needs (12, 13). Over the past eight years, the regulatory systems of 26 sub Saharan African countries were assessed (13).

To provide data and information on quality medicines regulation, access to essential medicines and the rational use of medicines, tools have been developed and systems established by the WHO to regularly collect and publish data on medicines situations in member countries (3-5). The WHO uses three groups of indicators to assess pharmaceutical systems. Level 1 indicators measure core structures and processes through key informant interviews (5, 14). Level II indicators which are mainly obtained through household and health facility based surveys, assess availability and affordability and geographical accessibility to key medicines and the rational use of medicines. Finally, level III indicators are more detailed and use an expanded list of indicators for key areas of the pharmaceutical sector. For example, medicine pricing, medicine supply management, rational drug use and regulatory capacity assessment all have specialised tools for data collection (5-7, 14).

The WHO carried out a Level I survey in 109 countries in 1999. In 2003 levels I and II studies were carried out in 140 countries while another level I survey was completed in 2007 in 156 countries (6-8). In addition to these surveys are the multi-country study on effective drug regulation in 2002 in 10 countries and the 2010 country profile study of which the regulatory section is the focus of this report (9, 10).

2.1 The 2004 level I, 2003 levels I and II, and the 2007 level I surveys

The 1999 level I survey was used in the production of the second edition of the World medicine situation report which was published in 2004 (2, 6). The survey showed that though many countries had a medicines regulatory authority and a formal requirement for registering medicines, less than one in six WHO member states had a well developed regulatory system (2). Also, the rate of inspection of manufacturing and distribution were 51 and 60% respectively in low income countries, 55 and 57% in middle income countries and 57 and 47% in high income countries. Regulation of drug promotion was least in low income countries (40, 49 and 51% in low-, middle-, and high income countries respectively). The survey identified over-concentration on pre-market evaluation rather than post market monitoring and giving significant attention to drug registration with little attention to the regulation of distribution as common imbalances in regulatory practice (2).

Data for the 2003 level I indicators were provided by the Ministries of Health of 140 (57 low income, 65 middle income and 18 high income) countries while the more detailed level II indicators were collected by 26 (15 low income, and 11 middle income) countries (7). The level II indicators measured the availability of essential medicines, medicine prices, stock out duration, adequacy of storage conditions, affordability, prescribing and dispensing habits, and presence of guidelines in public health facilities and their dispensaries, pharmaceutical warehouses, and sample private drug outlets. The outcomes of the 2003 survey are summarized below:

1. Most of the countries had national medicines policy (86% for low income countries, 69% of middle income countries, and 48% of high income countries) More than 75% of the medicine policies in each country category were updated within the last 10 years before the survey
2. At least 90% of countries in each category had a regulatory authority. Countries at all income levels had a comprehensive legal regulatory framework that covered all aspects of the pharmaceutical sector i.e. marketing authorization, manufacturing of medicines, distribution of medicines, promotion and advertising of medicines, importation of medicines, exportation of medicines, licensing and practice of pharmacy, empowerment to enter premises, and the requirement for regulatory transparency.
3. While most of the countries inspected importers, manufacturers, distributers and pharmacies, site inspection was less frequent in low income countries
4. The rates of monitoring of adverse drug reactions were, 33, 62, and 86% for low-, middle- and high income countries respectively, indicating low frequency on monitoring adverse drug reactions (ADRs) in low income countries.

5. In the area of post registration testing, low income countries tended to collect fewer samples and reported higher rates of products failing testing.
6. Computerized medicine registration systems existed in 49% of low income countries, 51% of middle income countries and 72% of high income countries.
7. Eighty percent of middle and low income countries have patent protection for pharmaceuticals compared to only 50% of low income countries. A third of low income countries and half of middle income countries reported having legislations supporting parallel importation compared to 60% in high income countries.

Data for the 2007 WHO level 1 study were obtained by sending questionnaires to countries via email to which 156 countries responded electronically (8). The countries were also categorized into low- middle and high income countries. The study reported similar results as in the 2003 survey described above. Below are some highlights of the results.

1. Ninety four percent of low, 84% of middle and 74% of high income countries had an official or draft national NMP. However the percentages of countries that had updated their NMPs 5years prior to the study were lower: 23, 44 and 54% for low, middle and high income countries respectively. The probability of having an NMP decreased with increasing country income level while the probability of updating NMPs 5years prior to the survey increased with increasing income level.
2. The proportion of countries that carried out indicator assessments for the overall pharmaceutical situation within five years prior to the study also increased with increasing country income level - 37, 48 and 49% for low, middle and high income countries respectively.
3. Ninety percent of countries had legal provisions for establishing MRAs while 89% of countries had formal DRAs.
4. Government budgets were identified as the main source of funding for MRAs (88% of countries). In addition, 73% of MRAs charged medicines registration fees.
5. Ninety one percent of countries had legal provisions to inspect premises, however, the presence of written guidelines for inspection of the various pharmaceutical providers were quite lower - 79, 77, 74, and 81% for manufacturers, wholesalers and distributors, importers and exporters, and retail distributors and pharmacies.
6. Ninety seven percent of countries had legal provisions for the control of narcotics while all the countries were signatories to the international convention on the control of narcotics.
7. Eighty seven percent of samples were tested in government quality control laboratories making government labs the most commonly used.

8. From 2003 to 2007, the proportion of countries having a computerized medicines registration system increased from 49 to 54%, 52 to 73% and 72 to 91% in low, middle and high income countries respectively.
9. Also the number of ADR monitoring systems in low income countries increased from 33% in 2003 to 50% in 2007 (7, 8).

2.2 The 2002 Multi-country study on effective drug regulation

The multi-country study on effective drug regulation was carried out in 10 countries in 2002 (9). The 10 countries were Uganda and Zimbabwe from the Africa region of the WHO, Cuba and Venezuela from the region of the Americas, Cyprus and Tunisia from the Eastern Mediterranean region, Estonia and Netherlands from the European region Malaysia from the South East Asia region and Australia from the Western Pacific region. The aim of the multi-country study was to compare, contrast and synthesize country experience in medicine regulation and draw generic conclusion from which other countries can learn (9). The legal and organizational structures were mapped out in the selected countries to determine whether a regulatory function exists and how these functions are executed with the available resources. The study was carried out by independent national investigators who collected data between 1998 and 1999 through key informant interviews using a standard questionnaire and archival study of relevant documents such as drug laws and DRA annual reports. The study frame work covered the key components of drug regulation indicated below:
Administrative elements: Policies, legislations, regulations, human resources finance, infrastructure.
Technical elements: Standards, specifications, guidelines, and procedures
Regulatory functions: licensing of premises, practices and persons, inspection of manufacturers and distributors, product assessment and registration, monitoring and quality of drugs, control of drug promotion and advertising, and adverse drug reaction monitoring.
Level of regulation: Whether the regulation is based on central, state/province, district or community levels.

The authors of the study identified the following as challenges to drug regulation;
Regulatory gaps: legislation does not cover all areas of pharmaceutical activity in the 10 countries. For example some countries omit traditional and herbal medicines and products imported by the government from regulatory control.
Accountability and transparency of DRAs: Fragmentation and delegation of regulatory responsibilities make co-ordination difficult, results in waste in resources and confrontation. Conflict of interest is also a challenge with DRAs that perform non-

regulatory functions as well. For example, DRAs responsible for non regulatory functions like manufacturing and procurement.
Human and financial resources constraints and
Balance of priorities: The regulation of distribution and post marketing surveillance are not given the same priority as the regulation of product registration.

2.3 The 2010 country profile pilot study design process and method

During 2011, the WHO Medicines Department plans to support as many WHO Member States as possible to develop national pharmaceutical country profiles. The 2010 country profile pilot study was therefore carried out as a precursor to the development of pharmaceutical profiles for all member countries. The pilot study involved 13 countries (10), chosen to provide a fair representation of the geographical regions of the WHO, low, middle and high income economies as well as large and small countries. The main tool used for collecting data on the 13 countries involved in the 2010 country profile pilot study was a data collection instrument which assessed indicators divided under the following in eight sections: health and demographic data, health services, policy issues, regulation, medicines financing, procurement and distribution of pharmaceuticals in the public sector, selection and rational use of medicines, and household data (access to medicines). The indicators included WHO levels I, II and III indicators. The aim of this country profile exercise was to collect existing data in a common format and in a single document.

The instrument and its glossary were developed by the Essential Medicines and Policy Department (EMP) of the WHO in conjunction with Harvard Medical School. The documents were later reviewed in March 2010 by a committee made up of representatives from Health Action International (HAI), WHO regional offices, Harvard Medical School, Medicines Transparency Alliance, EMP technical staff, Oswaldo Cruz Foundation from Brazil, University of Utrecht, the Austrian Federal Institute for Health Care and WHO country officers from the study countries. The glossary explains the information sought by the survey instrument and also provides possible sources from which the data requested by the survey instrument could be obtained. A data collection manual and the glossary to the instrument were provided to the countries guide data collection.

The instrument was prefilled with information already available to the WHO headquarters and then sent out to the WHO country officers in the study countries electronically in a Microsoft Word file. The data obtained was secondary data from government and other documents. The countries were asked on the data collection

instrument to indicate the year and source of their data, attach the relevant publications and provide links to other information available online.

A coordinator was nominated for each of the 13 pilot countries for the purpose of following up. The name and contact address of each coordinator was put on the first page of the instrument. Space was also provided for the addresses of individuals completing sections of the instrument. During the period of the study, follow-up correspondences were made to remind the co-ordinators to submit the instrument and other supporting documents. Governments of the study countries were involved in the completion of the instrument. The completed instrument was then certified by the Ministry of Health of the corresponding country, giving formal permission for its publication and use in additional analysis.

Only 12 out of the 13 countries submitted their data in time to be included in this analysis.

3.0 Methods

Data for this report was obtained by three main methods: reviewing the answers provided by the countries on the 2010 pharmaceutical country profile pilot study instrument, reviewing the other supporting documents submitted by the study countries and by browsing the websites of the MRAs and other relevant websites for information.

Reviewing the 2010 pharmaceutical country profile survey results: Data from the 2010 pharmaceutical country profile study which had been recorded in Microsoft Excel, was thoroughly cross checked with the original instrument to ensure that all the indicators on the instrument were transferred into the Excel program. The results in the Excel spread sheet were then reviewed item by item. Using Excel formula functions, the proportion of countries in each category of response were calculated.

Data was mainly obtained from the regulatory section of the country profile instrument. The other seven sections of the instrument were also reviewed for any regulatory related information. The socio-economic indicators such as total population and GNI were obtained from the health and demographic data section of the survey. Statistics on the pharmaceutical sector of the countries such as total pharmaceutical expenditure and number of licensed pharmacies were pooled from the health services and policy issues sections of the survey instrument.

Reviewing documents attached to the 2010 country profile study instruments: After summarizing the results of the excel spread sheet, the documents attached to the results by the study countries were reviewed. The reviews of these documents were carried out for three main purposes: i) to obtain new information on the study countries that was not provided by the answers in the instrument, ii) to verify data on the instrument provided by the study countries.

Pooling information from relevant websites: The URLs that the study countries provided were visited to confirm these URLs and the information they showcased. Each of the 12 websites of MRAs was also visited. A list of the websites visited is provided in annex 1.

4.0 Results

The findings on the regulatory system of the twelve study countries which completed and returned the survey instruments on time are explained under various headings below.

4.1 Profile of the countries

The socio-economic profile of the study countries: Table 4.1.1 (page 21) shows the general economic and health backgrounds of the 12 study countries. The countries were selected from all the six WHO regions - Kenya and Nigeria from the African region, Argentina and Suriname from the Region of the Americas, Pakistan, Sudan and Jordan from the Eastern Mediterranean Regional Office, Armenia and Austria from the European Region, Maldives and Sri Lanka from South East Asia and China from the Western Pacific region. Kenya was the only low income country among the study countries while Nigeria, Jordan, Pakistan, Sudan, Armenia, Sri Lanka and Maldives constituted the lower middle income countries. The upper middle income countries included Argentina and Suriname while Austria was the only high income level country (15). The 13 pilot countries were purposively selected to provide a range of possible country situations. However, with such a selection method and the small sample size, the sample selected cannot be considered representative of the situations in all member countries or WHO regions.

The total population of the study countries varied from 306,000 (Maldives) to about 1.3 billion (China). China had the largest area of 9,600,000km² followed by Argentina and Sudan with 2,767,000 and 2,500,000 respectively. Armenia had the least size of 29,800km², followed by Sri-Lanka with 65,610km². However in terms population density Maldives, the least populated country, and Suriname the second least populated country, had the lowest of 3 persons per km². These two countries may therefore represent the most sparsely populated countries. Sri Lanka may represent the most densely populated country with a density of 308 followed by Pakistan with a density of 204 persons/km².

China had the highest total GNI ($ 3,929 billion) while the GNI per capita was highest in Austria $ 36,040 billion. On the other hand, Maldives had the lowest total GNI while Pakistan had the lowest GNI per capita. Life expectancy for males and females varied from 78 and 83 years respectively in Austria to 49 years for both males and females in Nigeria. Under five mortality also varied from 4 in Austria to 90 deaths per 1000 live births in Pakistan.

Table 4.1.1, General socio-economic background of the study countries

Country	Region	Total Population (,000)	Life expectancy (Male/Female) / years	Under 5 mortality rate/ 1000 live births	Total GNI (billion $)	GNI per capita (US $)	Area of country/ km²	Population density (number of persons /km²
Argentina	America	40,518 (2010)	72 / 79 (2010)	15 (2008)	292	7,200	2,766,890	15
Armenia	Europe	3,002 (2007)	66 / 73 (2007)	24 (2007)	10	3,350	29,800	101
Austria	Europe	8,355 (2008)	78 / 83 (2008)	4 (2007)	301	36,040	83,872	100
China	Western Pacific	1,336,317 (2007)	72 / 76 (2010)	21 (2010)	3929	2,940	9,600 000	139
Jordan	Eastern Mediterra-nean	5,924 (2007)	70 / 74 (2007)	20 (2007)	20	3,310	88,778	67
Kenya	Africa	38,765 (2008)	53 / 55 (2008)	74 (2008)	61	1580	582,646	67
Maldives	South-East Asia	306 (2007)	73 / 74 (2008)	14 (2008)	1	3,630	110,940	3
Nigeria	Africa	151,212 (2008)	49 / 49 (2008)	186 (2008)	175	1,160	923,768	164
Pakistan	Eastern Mediterr-anean	163,902 (2007)	63 / 64 (2007)	90 (2007)	161	980	803,940	204
Sri Lanka	South-East Asia	20,217 (2008)	68 / 76 (2006)	13 (2003)	31	1540	65,610	308
Sudan	Eastern Mediterr-anean	41,348 (2008)	57/58 (2006)	112 (2006)	63	1,511	2,500 000	17
Suriname	America	510 (2007)	66 / 73 (2007)	19 (2010)	2	4,679	165,000	3,091

The pharmaceutical profile of the study countries: Table 4.1.2 (page 22) summarizes the pharmaceutical profiles of the countries as they existed during the period of the study. Total pharmaceutical expenditure (TPE) ranged from $ 12m in Maldives (lowest) to $ 59bn in China (highest). However, TPE per capita ranged from $ 3.90 in Nigeria to $ 601 in Austria, the only high income country among the study countries. Figure 4.1.1 (page 23) shows a chart of TPE per capita by country.

Table 4.1.2, Background of the pharmaceutical sector in the study countries

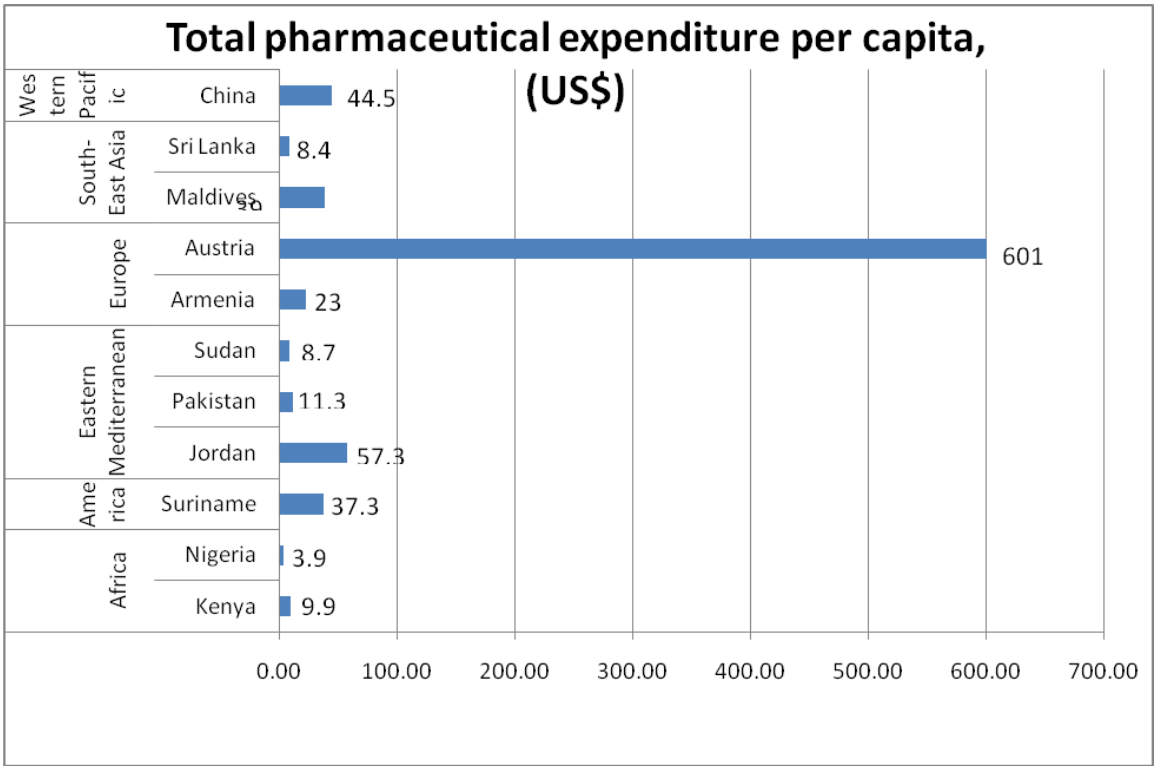
Region	Country	TPE (in million US $)	TPE per capita, (US$)	TPE per capita/ GNI per capita ratio(%)	Total number of licensed pharmacies	Number of licensed pharmacies per 10,000 persons	Number of licensed pharmacies per 1000km²	Total number of licensed pharmaceutical manufacturers	Total number of registered products
Africa	Kenya	372	9.9	0.6%	-	-	-	45	13,000 (2010)
	Nigeria	574	3.9	0.3%	3,601	0.2	3.9	146	1870 (2010)
America	Argentina	-	-	-	-	-	-	402	55,664 (2010)
	Suriname	19	37.3	0.8%	27	0.5	0.2	3	2777 (2010)
Eastern Mediterranean	Jordan	344	57.3	1.7%	1,810	3.1	20.4	16	7,700
	Pakistan	1,844	11.3	1.2%	7,000	0.4	8.7	478	50,000 (2010)
	Sudan	363	8.7	0.6%	2,306	0.6	0.9	19	3,702 (2009)
Europe	Armenia	76	23.0	0.7%	1560	5.2	52.3	14	3,900 (2007)
	Austria	4,997	601.0	1.7%	1,252	1.5	14.9	220	13,168 (2010)
South East Asia	Maldives	12	39.0	1.1%	243	7.9	2.2	1	852 (2010)
	Sri Lanka	168	8.4	0.5%	2,950	1.5	45.0	8	6149 (2010)
Western Pacific	China	59,425	44.5	1.5%	-	-	-	7161	176,000 (2007)

- = data not available

Differences also existed within the same WHO regions. For example, TPE per capita varies from about $ 9 in Sudan to $ 57 in Jordan within the Eastern Mediterranean region while between the two countries in the European region, Armenia and Austria, TPE per capita varied substantially from $ 23 to $ 601 respectively. The ratio of TPE per capita to GNI per capita shows that countries with the highest GNI per capita did not always have the highest pharmaceutical expenditure per capita. For example, Jordan and Austria both had the same TPE/GNI per capita ratio of 1.7% (the highest) though the GNI per capita in Austria was about ten times that of Jordan. Nigeria spent the least (0.3%) of its GNI per

capita on pharmaceuticals. Pakistan, the country with the lowest GNI per capita spent 1.2% of its GNI per capita on pharmaceuticals, the third highest TPE/GNI per capita ratio among the study countries.

Figure 4.1.1 A chart of TPE per capita for the study countries



The total number of pharmacies in each of the 9 study countries that reported this figure ranges from as low as 27 in Suriname to as high as 7,000 in Pakistan. Nigeria had the least ratio of the number of pharmacies per 10,000 persons – 0.2 while Maldives, the country with the least population had the highest – 7.9. Assuming an even geographical distribution of the population and the number of pharmacies within a country, which might not be the case, geographical access to pharmacies could be highest in Maldives.
The number of licensed pharmacies per 1000km² is lowest in Suriname (0.2) and highest in Armenia the smallest country and the country with the second highest number of pharmacies per 10,000 persons.

Maldives had only one local manufacturer and the lowest number of registered products. China, the most populous study country has the highest number of local pharmaceutical manufacturers – 7,161, and the highest number of registered products, 176,000. Maldives had the lowest number of registered products.

4.2 Regulatory framework and capacity of the countries

Framework of MRAs: Table 4.2.1 (below) describes the framework of the MRAs in the study countries. All of the 12 countries had legal provisions establishing the powers and responsibilities of their MRAs. However, only seven reported assessing their regulatory system within five years prior to the study.

Table 4.2.1, Legal framework of MRA's

Indicators	Argentina	Armenia	Austria	China	Jordan	Kenya	Maldives	Nigeria	Pakistan	Sri-Lanka	Sudan	Suriname	Number responding 'yes'
Existence of legal provisions establishing the powers and responsibilities of MRA	●	●	●	●	●	●	●	●	●	●	●	●	12/12
An assessment of medicines regulatory system in the last 5 years	●	●	●	□	□	●	□	●	□	□	●	●	7/12
Existence of formal code of conduct for medicine regulation staff	●	●	●	-	●	●	-	●	●	●	●	□	9/10
MRA uses a computerized information system	●	●	●	●	□	●	●	●	□	□	●	●	9/12
MRA has its own website	●	●	●	●	●	●	□	●	●	□	●	□	9/12
MRA is involved in harmonization and collaboration initiatives	●	●	●	●	●	●	□	●	●	□	□	●	9/12

● = yes □ = no - = information not available

The countries which had not reviewed their regulatory systems within five years prior to the study included China, Jordan, Maldives, Pakistan and Sri-Lanka. In addition to these legal provisions, nine countries had official code of conducts for medicines regulatory staffs.

With the exception of Jordan, Pakistan and Sri-Lanka, all the countries used computerized information management system to store and retrieve information their

regulatory activities. Also, the MRAs in Sri-Lanka, Maldives and Suriname did not have their own websites. This is surprising especially in the case of Sri-Lanka because of the relatively high level of development in information technology in that country. The rest of the study countries had their own websites for MRAs (Annex 1). Nine of the MRAs were involved in harmonization and collaborating initiatives. The list of collaboration partners provided by these countries included: the WHO, domestic provinces, European Medicines Agency, the Africa Medicines Registration Harmonization, the Harmonization of Medicines Regulation in East African Countries, the West African Drug Regulatory Authority Network and the Pan American Network on Drug Regulatory Harmonization. MRAs in Maldives Sri-Lanka and Suriname were not involved in any collaborating activities.

Funding of MRAs: Table 4.2.2 (below) displays how MRAs of the countries surveyed were funded. With the exception of Armenia and Kenya, All of the MRAs received funds from the regular budget of their governments. Seven MRAs (Argentina, Armenia, Austria, Jordan, Kenya, Nigeria and Sudan) were partially funded from fees for services. Four out of these seven countries (Argentina, Armenia, Austria and Kenya) kept the revenues generated from their regulatory activities. This would likely make these MRAs more autonomous in their regulatory activities.

Table 4. 2.2, Funding of MRAs

Indicators	Argentina	Armenia	Austria	China	Jordan	Kenya	Maldives	Nigeria	Pakistan	Sri-Lanka	Sudan	Suriname	Number responding 'yes'
MRA gets funds from regular budget of government	●	□	●	●	●	□	●	●	●	●	●	●	10/12
MRA is funded from fees for services	●	●	●	□	●	●	□	●	□	□	●	□	7/12
MRA receives funds from other sources	●	●	□	□	□	●	●	□	●	●	●	●	8/12
Revenues from regulatory activities are kept with the regulatory authority	●	●	●	□	□	●	□	□	□	□	□	□	4/12

● = yes □ = no - = information not available

In addition to government funding or fees for services, or both, eight MRAs received funding from other sources. The other sources of funding mentioned by the countries included the WHO, the European Commission, the Global Fund, the pharmaceutical industry and grants and donor funds through the MOHs. China was the only country that relied solely on government funding which could make the MRA of the country free from regulatory provider capture but not free from governmental control. On the other hand, Argentina was the only country that obtained funds from all the three major sources described. Apart from China, all the countries had at least two sources of funding.

Autonomy of MRAs: According to the instrument and the manual used in the data collection, an MRA is considered part of the MOH if employees of the MRA are MOH employees and the line items of the MRA's budget are directly controlled by the MOH. If staffs are employed outside the regular government structure the MRA is considered semi-autonomous. Based on this definition, Argentina, Austria Jordan and Sudan classified their MRA as semi-autonomous while China and Nigeria classified their MRAs as both semi-autonomous and under the MOH. The remaining six countries had their MRAs under the MOH.

4.3 Marketing authorization

Table 4.3.1 (page 27) shows the compliance of the different countries with the legal provisions on Marketing Authorization (MA). Legal provisions requiring for the publication of Summary Product Characteristics (SPC) of registered medicines was the least available legal provision on MA in the study countries (5 out of 11 respondents). Legal provisions requiring the declaration of potential conflict of interest for experts involved in the assessment and decision making during drug registration, a good indicator of transparency, was also less common in the study countries (six out of eleven respondents indicated having this provisions).

All the twelve countries had legal provisions requiring marketing authorization of all pharmaceutical products as well as publicly available criteria for assessing applications for marketing authorization. Eleven out of the twelve countries (with the exception of Argentina) had legal provisions requiring expert involvement in the MA application process. However three of the countries – Kenya, Sri-Lanka and Jordan did not have any legal provision for publishing a list of registered pharmaceutical products with defined periodicity. Out of the nine countries that had this provision, only Armenia and Maldives indicated that this list is updated monthly, while Argentina and Austria only described the frequency updating the list as "continuous". China and Pakistan did not provide the URL to this list while in Suriname, the list was not available online but could be obtained upon

a request to the Registration Bureau. Argentina, Armenia and Austria, Maldives, Nigeria and Sudan provided URLs to their list (Annex II).

Table 4.3.1, The existence of legal provisions on marketing authorization

	Number responding 'yes'	Total number of respondents
Existence of legal provisions requiring marketing authorization of all pharmaceutical products	12	12
Publicly available criteria for assessing applications for marketing authorization of pharmaceuticals	12	12
Existence of legal provision requiring MRA to make available a list of registered pharmaceuticals with defined periodicity	9	12
Registration of medicines by their INN name or Brand name + INN	12	12
Legal provisions requiring paying a fee for medicine registration	12	12
Legal provision requiring the provision of information about variations in existing market authorization	12	12
Legal provisions requiring the publication of Summary Product Characteristics of registered medicines	5	11
Legal provisions requiring expert committee involvement in MA application process	11	12
Certificate of Pharmaceutical products in accordance with WHO certification scheme required as part of the MA application	8	11
Legal provision requiring the declaration of potential conflict of interests for experts involved in assessment and decision making for registration	6	11
Legal provisions allow applicants to appeal against MRA decisions	9	11

Legal provisions requiring for the registration of medicines by INN name or Brand name with INN name, as well as provisions for the payment of a fee for medicine registration and for the provision of information by the manufacturer about any variation in existing market authorization existed in all the 12 countries.

Medicines registration fees: The range of the fee for registering a new chemical entity ranges from $18 to $15,000, while the fee for registering a generic product ranges from 18 to $ 8,000 in Suriname and Pakistan respectively (Table 4.3.2 page 27). Apart from Kenya in the Africa region, Suriname in the America region and Sudan in the Eastern Mediterranean region where the fees for registering NCEs are the same as those for registering generics ($1,000, $18 and $600 respectively), the fee for NCEs is higher than

generics in the other countries. The ratio of the fee of registering an NCE to that of a generic thus ranges from 1 to 9 (Argentina). On average the fees for registering NCEs was three times higher than the fees for registering generic products. The official time limit for assessing market authorization varied from three months in Nigeria to 14 months in China with an average of 7 months.

Table 4.3.2, Medicines registration fees and time limits

Region	Country	Fee per application for NCE ($)	Fee per application for a multisource pharmaceutical product	Ratio of NCE to Generic registration fees	Official time limit for the assessment of MA (months)
Africa	Kenya	1000	1000	1.0	6
Africa	Nigeria	4,667	-	-	3
America	Argentina	2,308	256	9.0	4
America	Suriname	18	18	1.0	6
Eastern Mediterranean	Jordan	2119	847	2.5	6
Eastern Mediterranean	Pakistan	15,000	8,000	1.9	6
Eastern Mediterranean	Sudan	600	600	1.0	12
Europe	Armenia	4800	1900	2.5	6
South-East Asia	Maldives	39	-	-	-
South-East Asia	Sri Lanka	442	88.5	5.0	-
Western Pacific	China	6661	-	-	14

- = information not available

Figures 4.3.1 and 4.3.2 (page 29) show a plot of GNI per capita versus the fees for registering NECs and generics respectively. Though similar trends are observed in both graphs, there is no clear correlation between GNI per capita and registration fees. For example, the highest fees for registering NCEs and generics ($15,000 and $8,000 respectively did not correspond to the highest or the lowest GNI per capita. Also the lowest NCE and generic registration fees ($18) neither corresponded with the lowest nor the highest GNI per capita.

Figure 4.3.1 Registration application fee for NCE (originator products) versus GNI per capita (US $)

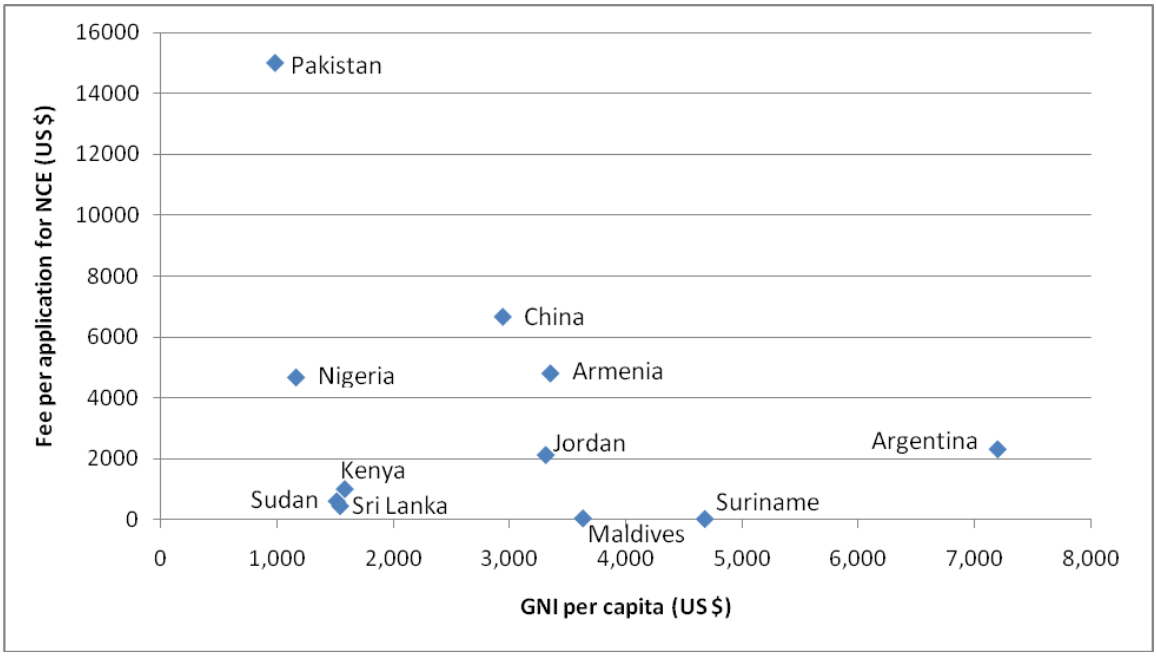
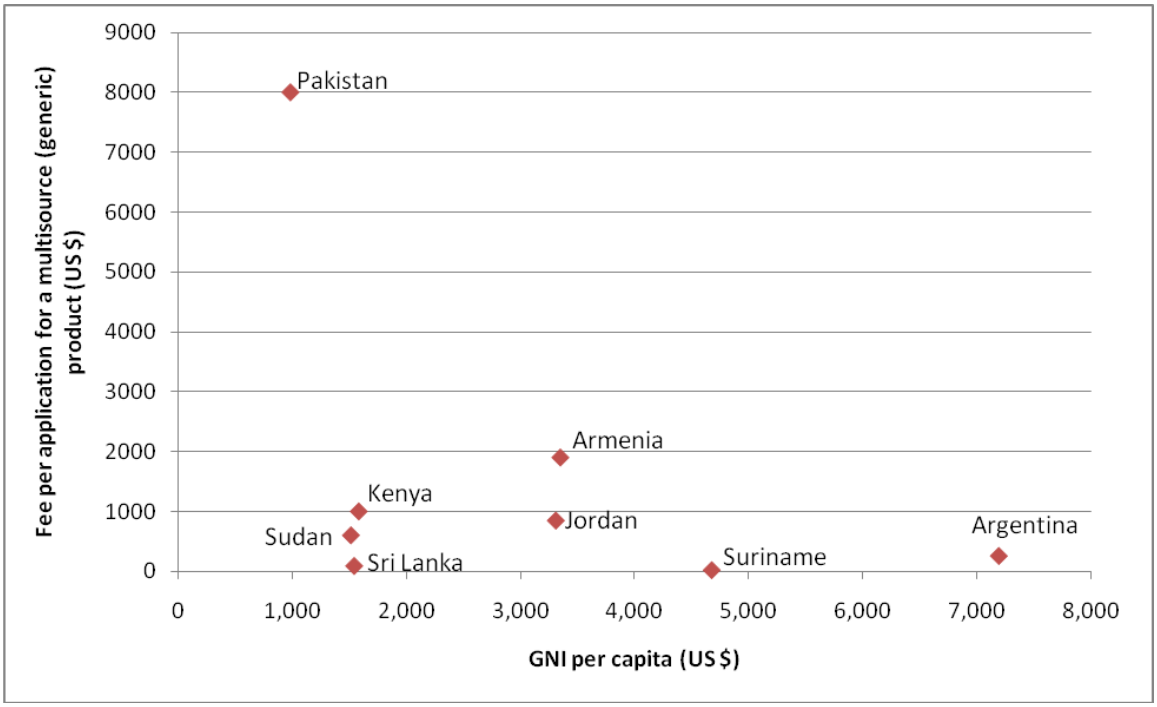


Figure 4.3.2 Registration application fee for generic versus GNI per capita (US $)



4.4 Regulatory inspection

Legal provisions on regulatory inspection: Table 4.4.1 (below) presents the existence of legal provisions for regulatory inspection in the study countries. All of the 12 countries had legal provisions permitting inspectors to inspect premises as well as provisions making inspection a pre-requisite for licensing of facilities.

Table 4.4.1 The existence of legal provisions on regulatory inspection

	Number responding 'yes'	Total number of respondents
Legal provisions for the appointment of government pharmaceutical inspectors	11	12
Legal provisions permitting inspectors to inspect premises	12	12
Legal provision requiring inspection to be performed	11	12
Inspection is a pre-requisite for licensing facilities	12	12
Inspection requirements same for both public and private facilities	9	10

Among the 12 countries, only China did not report having legal provisions for the appointment of government pharmaceutical inspectors. Suriname did not have legal provisions requiring inspection to be performed while the rest of the countries did. Nine respondents indicated the same inspection requirements for both public and private pharmaceutical facilities. These requirements are not the same in Sri-Lanka.

Inspection capacity: Table 4.4.2 (page 31) summarizes the number of inspectors, licensed pharmacies and manufacturing companies in the study countries. Out of the 10 countries that reported the number of government pharmaceutical inspectors, Pakistan had the highest (305) while Sri-Lanka had the least. Pakistan also had the largest number of licensed pharmacies, 7,000, while Suriname had the least, 27. The ratio of the number of inspectors to 100 pharmacies was highest in Nigeria, which is relatively favorable to effective inspection compared to the lowest ratio of 0.1 in Sri-Lanka.

China had the highest number of pharmaceutical manufacturers but data on its number of inspectors was not available. Maldives had only one pharmaceutical manufacturer and therefore the highest number of inspectors per 10 manufacturers, i.e. 90. Nigeria reported the second highest number of inspectors per 10 manufacturers - 20. These ratios are relatively favorable compared to the low ratios of about 1 and 3 recorded in Argentina

and Sri-Lanka respectively. Jordan which reported having 17 inspectors indicated that 10 are for licensed pharmacies while 7 are for manufacturers.

Table 4.4.2, Number of inspectors, licensed pharmacies and manufacturing companies per country

Region	Country	Number of Government Inspectors	Number of licensed pharmacies	Number of inspectors per 100, licensed pharmacy	Number of licensed manufacturing companies	Number of inspectors per 10 manufacturers
Africa	Kenya	43	-	-	45	9.56
Africa	Nigeria	287	3,601	7.97	146	19.66
America	Argentina	45	-	-	402	1.12
America	Suriname		27	-	3	-
Eastern Mediterranean	Jordan	17	1810	0.94	16	10.63
Eastern Mediterranean	Pakistan	305	7,000	4.36	478	6.38
Eastern Mediterranean	Sudan	-	2306	-	19	-
Europe	Armenia	4	1560	0.26	14	2.86
Europe	Austria		1,252	-	220	-
South-East Asia	Maldives	9	243	3.70	1	90.00
South-East Asia	Sri Lanka	3	2950	0.10	8	3.75
Western Pacific	China	-	-	-	7161	-

4.4 Import control

Nigeria did not provide any information on its legislations governing import control. All the other eleven respondents had legal provisions requiring authorization before importing medicines as well as legal provisions requiring sampling of imported products for testing. Sudan and Jordan did not have any legal provision requiring the importation of medicines through authorized ports of entry. All of the 10 respondents confirmed the presence of legal provisions allowing the inspection of imported products at the

authorized ports of entry. In general, legal provisions on import control existed in all the respondent countries (Table 4.5.1 page 32).

Table 4.5.1, Legal provisions for import control

	Number responding 'yes'	Total number of respondents
Legal provisions requiring authorization to import medicines	11	11
Legal provisions allowing sampling of imported products for testing	11	11
Legal provisions requiring importation of medicines through authorized ports of entry	9	11
Legal provisions allowing inspection of imported products at the authorized port of entry	10	10

4.6 Licensing

Manufacturing: All of the 12 study countries had legal provisions requiring manufacturers to be licensed (Table 4.6.1 below). Apart from in Suriname all of the countries also had legal provisions on compliance with GMP. However the publication of GMP requirements by governments in the study countries, a good indicator of transparency in the regulation of the medicines was poorly done. In addition to providing the needed transparency in drug regulation, the publication of GMP requirements may encourage enforcement of GMP and improve compliance by the manufacturers. However, only 7 out of the 12 respondents indicated the publication of GMP requirements.

Table 4.6.1, Legal provisions on pharmaceutical manufacturing

	Number responding 'yes'	Total number of respondents
Legal provisions requiring manufacturers to be licensed	12	12
Legal provisions requiring compliance with GMP	11	12
Government publishes GMP requirements	7	12

Distribution: All the countries had legal provisions requiring wholesalers and distributors to be licensed. Legal provisions for licensing private pharmacies also existed in all the countries. However Kenya and Sri-Lanka had no legal provisions requiring public pharmacies to be licensed. This information was not available on Pakistan. The remaining nine countries had legal provisions for licensing public pharmacies. The major area of

concern was the existence of legal provisions on Good Distribution Practice (GDP). Unlike GMP, for which all the countries had legal provisions requiring compliance (Table 4.6.1 above), legal provisions requiring compliance with GDP (Table 4.6.2 page 33) existed in only about half of the study countries. Armenia, Maldives, Nigeria and Suriname did not have any provisions for wholesalers and retailers to comply with GDP though three of these countries had GMP requirements for manufacturers. Suriname was the only country which had neither GMP nor GDP provisions. The publication of GDP requirements, also a good indicator of transparency and a probable step towards enforcement, was done in only six of the countries.

Table 4.6.2, Legal provisions on the distribution of pharmaceuticals

	Number responding 'yes'	Total number or respondents
Legal provisions requiring wholesalers and distributors to be licensed	12	12
Legal provisions requiring compliance with GDP	6	11
Government publishes GDP requirements	6	12
Legal provisions requiring private pharmacies to be licensed	12	12
Legal provisions requiring public pharmacies to be licensed	9	11

Other legal provisions on licensing: All countries had legal provisions requiring the licensing of pharmacists except Armenia (Table 4.6.3 below). Only two countries - Austria and Sudan publishes national good pharmacy practice guidelines and only four countries had legal provisions for publishing a list of different categories of pharmaceutical facilities (Armenia, Austria, Maldives and Pakistan). These show limited transparency as far as these provisions are concerned. Eleven out of the 12 countries had legal provisions requiring importers to be licensed.

Table 4.6.3, Other legal provisions on licensing.

	Number responding 'yes'	Total number of respondents
Legal provisions requiring pharmacists to be licensed	11	12
National Good Pharmacy Practice Guidelines are published	2	10
Legal provisions requiring the publication of a list of different categories of pharmaceutical facilities	4	8
Legal provisions requiring importers to be licensed	11	12

Section 4.7 Market control and quality control

Legal provisions and testing facilities: Table 4.7.1 (below) shows the conformity to legal provisions and the existence of facilities for market control and quality control in the countries. It is worth noting that all of the countries had a quality control laboratory and do not contract quality control services from other countries. Inspectors in all the 12 countries also collected samples for post marketing surveillance testing. Out of 11 respondent countries, only Sri-Lanka did not report having any legal provision on controlling the pharmaceutical market. Public availability of quality testing results was poor, indicating limited transparency. Only Austria and China claimed to make quality testing results publicly available. In Sudan, only recalled pharmaceutical products were publicly posted on the MRA website.

Table 4.7.1, Regulatory provisions and facilities for market control and quality control

	Number responding 'yes'	Total number of respondents
Legal provisions for controlling the pharmaceutical market	10	11
Laboratory exist in the country for Quality Control	12	12
Samples are collected by inspectors for post marketing surveillance testing	12	12
Results of quality testing in the past two years publicly available	2	10

Post marketing surveillance: Table 4.7.2 (below) shows the number of samples taken for testing and the proportion of samples that failed to meet quality standards in seven of the study countries.

Table 4.7.2, Testing of samples in the last two years

Country	Number of registered products	Number of samples taken for testing in the last two years	Number of samples tested in the past 2yrs that failed to meet quality standards	% samples failing testing in the past 2 years
Armenia	3,900	18	7	39
Austria	13,168	33	3	2
Jordan	7,700	16,049	176	1
Pakistan	50,000	60,000	1,194	9
Sri Lanka	6,149	1432	393	27
Sudan	3,702	365	42	12
Suriname	2,777	370	2	1

Data on the testing of samples in China, the country with the highest number of registered products was not available. Pakistan had the third highest number of products within the study countries (Table 4.1.2, page 22) and the highest among the six countries that reported their data on the testing of samples two years prior to the study.

It is therefore not surprising that Pakistan reported testing the highest number of samples (60,000) while Armenia, the country with the second least number of registered products after Suriname reported taking the least number of samples for testing. The number of samples taken for testing increased with the number of registered products. The failure rate of tested samples was highest (39%) in Armenia, the country with relatively fewer registered products. Suriname and Jordan recorded the lowest failure rate, which was of 1%.

4.8 Medicines advertising and promotion

Legal provisions on advertising and promotion: Table 4.8.1 (below) summarizes the existence of legal provisions on medicines promotion and advertizing in the study countries. All of the countries had legal provisions to control the promotion and advertising of prescription medicines. Also, legal provisions to prohibit direct advertizing of prescription medicines to the public existed in all countries except in Jordan and Suriname. While pre-approval for medicines advertising and promotional materials was a legal pre-requisite in all the other countries, this was not the case in Argentina and Suriname. Also Suriname had no guideline or regulation for the advertisement and promotion of non-prescription medicines. In general, legal provisions on advertising and promotion are least comprehensive in Suriname.

Table 4.8.1, Presence of legal provisions on medicines advertising and promotion

	Number responding 'yes'	Total number of respondents
Legal provisions to control the promotion and/advertising of prescription medicines	12	12
Legal provisions to prohibit direct advertizing of prescription medicines to the public	10	12
Legal provisions require pre-approval for medicines advertisements and promotional materials	10	12
Guidelines/regulations for advertising and promotion of non-prescription medicines	11	12

The institutions listed by the study countries for being responsible for regulating promotion and advertising of medicines included governments and MOHs and MRAs. In Nigeria, this responsibility is delegated to the MRA by the Minister of Health. Only

Jordan mentioned the pharmaceutical industry in addition to government as being responsible for the regulation of advertisement and promotion. Suriname did not report having any legal authority on the promotion and advertisement of medicines.

Code of conduct on promotion and advertising: All the study countries had national codes of conducts on advertisement and promotion except Armenia, Sri Lanka, Sudan and Suriname (Table 4.8.2, page 35 and annex V)

Table 4.7.2, Existence of a national code of conduct

	Argentina	Armenia	Austria	China	Jordan	Kenya	Maldives	Nigeria	Pakistan	Sri-Lanka	Sudan	Surname	No. of respondents	Number responding 'yes'
National code of conduct concerning advertising and promotion publicly available	●	□	●	●	●	●	●	●	●	□	□	□	12	8
Adherence to the code is voluntary	□	-	●	●	□	□	□	●	●	-	-	-	8	4
The code contains formal processes for complaints and sanctions	●	-	□	●	□	●	□	●	●	-	-	-	8	5
List of complaints and sanctions for the last 2years is publicly available	□	-	-	●	-	-	-	●	□	-	-	-	4	2

● = yes, □ = no - = information not applicable

Adherence to the code of conduct was compulsory in only four (Argentina, Jordan, Kenya and Maldives) out of the eight countries with the code of conduct. Also five out of the eight countries (Argentina, China, Kenya, Nigeria and Pakistan) with the code of conduct indicated the existence of formal processes for handling complaints and imposing sanctions. This means the remaining three countries either did not have room for handling complaints and imposing sanctions or these processes existed but were not formal. Also only China and Nigeria out of the five countries with formal processes for

complaints and sanctions, claimed to have made public the list of complaints and sanctions that took place 2 years prior to the study (specific references not provided). This level of transparency was missing in the other countries.

4.9 Clinical trials

Maldives did not respond to any of the questions on Clinical Trial regulation because clinical trials were not permitted in the country. Sri Lanka was in the process of drafting its legislations on clinical trials at the time of the study. The remaining ten countries had legal provisions requiring MRA's authorization for conducting clinical trials as well as legal provisions requiring authorization by an ethics committee or institutional review board of the clinical trials to be performed (Table 4.9.1 below). Out of these ten countries, Nigeria and Sudan did not have any legal provision that required the registration of the clinical trials into international, national or regional registries, while it is unknown if Argentina and Suriname had these provisions. Only Austria, China, Nigeria and Pakistan had legal provisions that required compliance of manufacturing investigational products with GMP.

Table 4.9.1, The existence of legal provisions on clinical trial

	Number responding 'yes'	Total number of respondents
Legal provisions requiring authorization for conducting Clinical Trials by the MRA	10	11
Legal provisions requiring authorization by an ethics committee or institutional review board of the clinical trials to be performed	10	11
Legal provisions requiring registration of the clinical trials into international/national/regional registry	6	8
Legal provisions for GMP compliance of investigational products	4	9
Legal provisions require sponsor, investigator to comply with good clinical practice (GCP)	6	9
National GCP regulations are published	4	9
Legal provisions permitting the inspection of facilities where clinical trials are performed	7	9

While Austria, China, Jordan, Kenya, Nigeria and Pakistan had legal provisions that required the sponsor and investigator to comply with Good Clinical Practice (GCP), only four of these countries (Austria, China, Nigeria and Pakistan) published these GCP regulations. This is an indication of inadequate transparency of information in the other countries. Seven out of nine countries reported the existence of legal provisions permitting the inspection of facilities where clinical trials were performed in their

countries. The main issues concerning clinical trials in the study countries included the non-existence of the necessary regulatory provisions, the lack of transparency in regulating clinical trials, and the practice of not requiring registration of clinical trials with the necessary authorities.

4.10 Controlled substances

All the study countries were signatories to the four international conventions on narcotic drugs (Table 4.10.1 below). For the 11 other countries that had this legal provision, only four (Armenia, Pakistan, Sri-Lanka and Suriname) have had their regulations reviewed by a WHO International Expert or Partner Organization to assess the balance between the prevention of abuse and access for medical need. (Annex III)

Table 4.10.1, Signatory of study countries to international conventions on controlled substances and national legal provisions on controlled substances

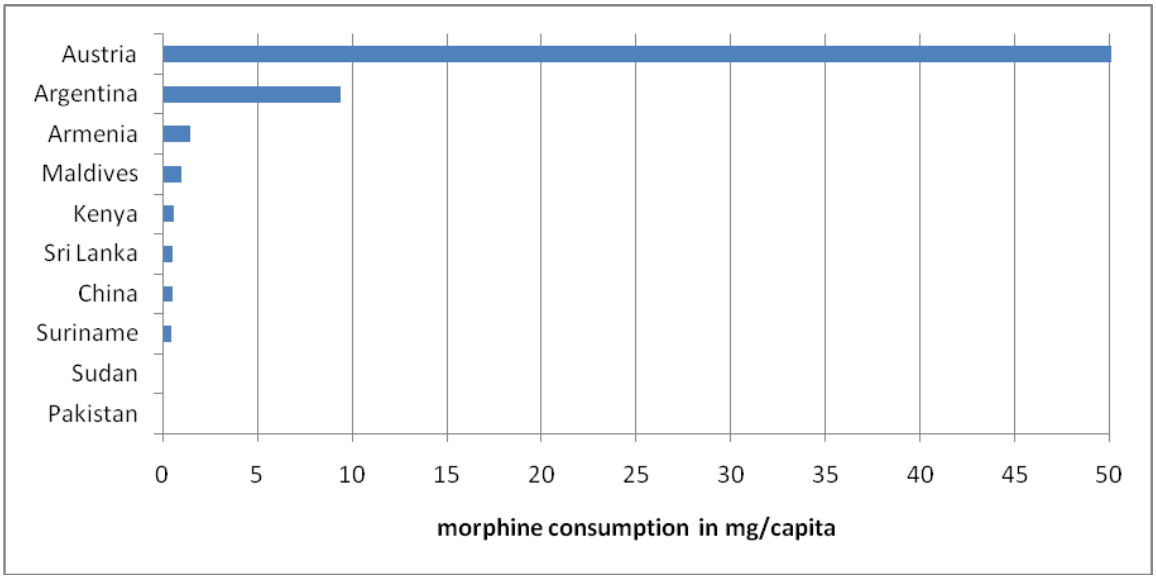
	Number responding Yes	Total number of respondents
Signatory to the single convention on Narcotic Drugs 1961	12	12
Signatory to the 1972 Protocol amending the Single Convention on Narcotic Drugs 1961	12	12
Signatory to the convention on Psychotropic substances 1971	12	12
Signatory to the United Nations Convention against the illicit Traffic in Narcotic Drugs and Psychotropic Substances 1988	12	12
Existence of national laws and regulations for the control of narcotic and psychotropic substances and precursors	11	12
The laws and regulations for the control of narcotic and psychotropic substances and precursors has been reviewed by a WHO International Expert or Partner Organization to assess the balance between the prevention of abuse and access for medical need	4	9

Consumption of controlled substances: Table 4.10.2 (page 39) shows the annual consumption in mg per capita of some controlled substances in the study countries that reported these figures. Austria reported the highest consumption of morphine (152mg per capita) while Pakistan reported the least (0.006). Austria again reported the highest consumption of Fentanyl while Kenya reported the least. Fig 4.10.1 (page 39) displays the consumption of morphine by country.

Table 4.10.2, Annual consumption of some controlled substances in mg per capita (ranked according to morphine consumption)

Country	Morphine	Fentanyl	Pethidine	Oxycodone	Phenobarbital	Methadone
Austria	152.36	2.035	1.03	4.818	-	6.864
Argentina	9.4	0.08	0.325	0.387	146.6	0.079
Armenia	1.42	0,003	0	0	15.4	0,81
Maldives	0.967	0.0017	3.4	0	25.64	6.54
Kenya	0.575	0.000071	1.215	-	-	-
Sri Lanka	0.49	0.0008	1.1	-	-	0.013
China	0.479	0.0061	1.7	0.0434	-	0.441
Suriname	0.4587	0.00313	0.3485	0	1848.91	0
Sudan	0.029	0.065	0.254	0	2.28	0
Pakistan	0.006	0.0018	0.006	0.00045	0.0106	-

Fig. 4.10.1, Graph showing the annual consumption of morphine in mg per capita by country



4.11. Pharmacovigilance

Legal provisions on pharmacovigilance: The Food and Drugs Authority in Maldives was in the process of establishing a pharmacovigilance unit during the time of the study. The country could not provide any information on its pharmacovigilance structure and activities. Compared to the existence of legal provisions on other sectors of pharmaceutical regulation such as the regulation of controlled medicines, licensing of premises, marketing authorization, and regulatory inspection which were discussed

earlier, the existence of legislations on pharmacovigilance in the study countries was less common. Legal provisions for pharmacovigilance activities existed in only five out of nine countries. Also, legal provisions requiring MA holder to monitor the safety of products and legal provisions on monitoring ADRs existed in only seven out of nine countries (Table 4.11.1 below). The other shortfalls that were identified included the publication of ADR bulletin in only 6 out of 11 countries and the few countries which used local pharmacovigilance data in making regulatory decisions 2 years prior to the study (3 out of 8 countries).

Table 4.11.1 Existence of legal provisions on pharmacovigilance

	Number responding 'yes'	Total number of respondents
Legal provisions in the medicines act provides for pharmacovigilance activities	5	9
Legal provisions requiring MA holder to continuously monitor safety of the products and report to the MRA	7	9
Legal provisions about monitoring ADR	7	9
National pharmacovigilance center linked to MRA	10	11
An analysis report by the pharmacovigilance center has been published within the last 2years	7	11
Pharmacovigilance center publishes an ADR Bulletin	6	11
Existence of an official standard form for reporting ADRs	11	11
Existence of a national ADR data base	10	11
ADR reports are sent to WHO database in Uppsala	9	11
ADRs monitored in at least one public health program	5	9
Feedback is provided to ADR reporters	10	11
ADR database is computerized	9	10
Medication errors are reported	9	11
Risk management plan is presented as part of product dossier submitted for MA	6	10
Regulatory decision based local Pharmacovigilance data in the past 2years	3	8
Institution of training courses in pharmacovigilance	10	10

The strengths identified on pharmacovigilance in the countries included the following: Ten out of 11 countries had pharmacovigilance centers linked to MRA. Official standard forms for reporting ADRs existed in all 11 respondent countries. Other positive findings included the existence of ADR databases and the provision of feedback to ADR reporters in 10 out of 11 countries, the submission of ADR reports to the WHO database and the computerization of ADR databases in 9 out of 10 countries. Furthermore, patient medication errors were reported in 9 out of 11 countries and there was the organization of training courses in pharmacovigilance in all the ten countries that reported on this subject.

Table 4.11.2, Persons/Professionals/Institutions reporting ADR within the past 2years

	Argentina	Armeria	Austria	China	Jordan	Kenya	Nigeria	Sri-Lanka	Sudan	Suriname	Frequency of reporting in the countries
Doctors	●	●	●	●	●	●	●	●	●	●	10/10
Pharmacists	●		●	●	●	●	●	●	●	●	9/10
Pharmaceutical companies	●	●	●	●	●	●	●	●			8/10
Nurses	●		●	●		●	●				5/10
Consumers	●	●		●			●				4/10
Others	●										1/10

Reporting of ADRs: Table 4.11.2 (above) displays the stakeholders in pharmaceutical regulation reporting ADRs in the study countries. Doctors reported ADRs in all the countries followed by pharmacists, pharmaceutical companies and nurses. Consumers were the least to report ADRs. Sudan and Suriname are the countries in which pharmaceutical no pharmaceutical company reported ADRs. These countries are 2 of the four countries which had no legislation that required the MA holder to be involved in post marketing surveillance. Pakistan, the only respondent country without a pharmacovigilance center linked to its MRA could not provide any information on who reported ADRs.

Table 4.11.3, Statistics on ADR reporting

Country	Number of ADR reports sent to the WHO in the past 2years	Number of reports in the ADR database	Number of ADR reports submitted in the past 2years
Argentina	500	32,330	9,560
Armenia	141	519	143
China		638996	
Jordan	36	400	40
Kenya	23	23	23
Nigeria	110	2,642	110
Sri Lanka	95	703	131
Sudan	50	160	
Suriname	220	260	260

Table 4.11.3 (above) summarizes the number of ADR reports sent to the WHO in the past 2 years, the number of reports in the national database of the study countries, as well as the number of ADR reports received in the past two years in the study countries. China, the country with the highest number of registered products had the highest number of ADR reports in its national database (638,996) while Kenya had the least of 23. Within the two years prior to the study, Argentina received the highest number of ADR reports – 9,560 while Kenya received 23, the least. Also, the number of ADR reports sent to the WHO varied from 500 in Argentina to 23 in Kenya.

Pharmacovigilance staff and training: China, the country with the highest population and number of registered pharmaceutical products recorded the highest number of pharmacovigilance staff, 50 (Table 4.11.4 below).

Table 4.11.4, Pharmacovigilance staff and number of people trained by country

Country	Number of pharmaco-vigilance staff	Number of people trained in pharma-covigilance the past 2years
Argentina	14	15
Armenia	3	720
China	50	
Kenya	3	350
Nigeria	7	250
Pakistan		300
Sudan	1	1
Suriname	1	100

Sudan and Suriname had only one pharmacovigilance staff. Armenia reported training the highest number of people in pharmacovigilance within 2years prior to the study. Argentina trained 15 while Sudan trained only one person. The number of trainings in Pakistan and Kenya and Suriname a new country were also relatively high, 300, 350 and 100 respectively.

5.0 Discussion

This section discusses the results of the 2010 pharmaceutical country profile survey according to the following major headings: the profile of the study countries, regulatory framework and capacity, marketing authorization, regulatory inspection, import control, licensing, market control and quality control, medicines advertising and promotion, clinical trials, controlled substances and pharmacovigilance. Where relevant and appropriate, these results are compared with the 2002 World Medicine Situation report, the results of the 2003 levels 1 and II surveys, and 2007 level I surveys, and the 2002 ten country study on effective drug regulation (6-9)**.**

5.1 The profile of the countries

Socio-economic profile of the countries: The study countries reflect the different geographical and economic status of WHO member countries. The wide variation in GNI per capita from $ 980 in Pakistan to $ 36,040 in Austria reflects the differences in quality of life of people and the resources likely to be available for regulation. For example the 2002 ten country study showed that the number of drug regulatory staff per 1 million population was 2 times higher in the high income countries than in the low income countries. The countries with high GNI per capita also had relatively higher life expectancy rates and lower under 5 year mortality rates. Austria, the country with the highest GNI per capita, had the lowest under 5 mortality (4 deaths per 1000 live births) and the highest life expectancy (78 and 83 for males and females respectively).

The 2002 ten country study also involved low, middle and high income countries. The size of the countries both in terms of population, size and geographical distribution are almost similar to the countries involved in the 2010 pilot study. Though the specific study countries involved in the two countries are different, the results of the two studies could be discussed bearing in mind the similar economic profile of the countries involved. The 2002 World Medicine Situation report, the 2003 level I and II study and the 2007 level I studies involved all member states of the WHO and hence presents a more representative sample.

The profile of pharmaceutical sectors of the study countries: Total pharmaceutical expenditure (TPE) per capita varied from $4 to $601 from Nigeria to Austria respectively. While this may not indicate the variations in the resources specifically allocated for pharmaceutical regulation in the study countries, it gives a clue to the amount of resources that could be available for the pharmaceutical regulation.

The total number of licensed pharmacies varied from 27 in Suriname to 7,000 in Pakistan while the number of licensed pharmaceutical manufacturers varied from one to 478. The total number of registered products also varied substantially: from 1,870 in Nigeria to 176,000 in China. The countries with more pharmaceutical facilities and products would need more regulatory resources such as regulatory staff, logistics for regular inspection and pharmacovigilance activities etc.

The pharmaceutical sectors of the study countries in the 2002 ten country study are comparable to that of the 2010 pilot study. The number of local pharmaceutical manufacturers also ranged from 10 in Estonia to about 325 in Australia. The number of registered pharmaceutical products for human use ranged from about 2000 in Cuba to about 32,500 in Australia. The number of pharmacies also ranged from about 500 to 7000. It is therefore worthwhile to compare the results of the two studies bearing in mind the similarities and the differences in the study countries.

5.2 Regulatory framework and capacity

The regulatory framework of MRAs: The existence of legal provisions establishing MRAs in all of the study countries is encouraging. However, only seven of the countries had assessed their regulatory system during the five years prior to the study. Periodic assessment of regulatory systems is necessary to enable the reformulation of policies based on the difficulties and successes of the implementation of the original policy (16). Also, it has been reported by the WHO that though national medicines legislations and regulations are often imported from other countries and they may not reflect national realities, they are often not regularly updated in many countries (17). Since pharmaceutical products, processes and practices change with time, regular assessment and updating of regulatory systems is important to keep up with the rapid scientific and technological change.

The 2002 ten country study showed a well defined legal status of MRAs in all of the study countries. The 2007 level I survey on the other hand showed legal provisions existed in 136 out of 151 member states. These figures indicate a generally good legal status of national MRA's in WHO member countries.

Not all the 12 countries had their own websites and only nine of the countries used computerized information systems. In the 2003 level I and II survey, 51 out of 136 responding countries had websites for their MRAs. A study by the WHO on the existence of MRA websites in its member countries also identified 51 sites, the same number reported in the 2003 survey (18). The results of he 2007 level I survey showed that 88 out

of 154 respondents indicated having publicly assessable MRA websites. This represents an increase of 37 in the number of MRAs with websites between 2001 and 2007. A 2009 study which was a follow-up to the 2001 WHO study on MRA websites identified 116 MRA websites out of 196 countries in 2009 (19). The quality of the websites, evaluated on the basis of user friendliness, site map, navigability, speed, update, links and nineteen other criteria, was also found to have improved. This shows that MRA websites are increasing in number and in quality.

With the internet becoming an important source of information for patients, health workers, and the industry (20), the quantitative and qualitative improvement in the websites of MRAs can be seen as a positive development. The WHO has undertaken to develop a model website for MRAs wishing to create or improve their websites (21). The WHO has also developed a practical guide help DRAs in implementing computer-assisted drug registration (22). These activities will further improve the use of information technology by MRAs in their regulatory activities.

Funding of MRAs: Though ten of the countries obtained funds from government, none of the MRAs except the Chinese MRA, relied solely on government funds. The other MRAs are either funded from user fees or with funds from other sources or both. While user fees are a reliable source of funding for MRAs, it has the potential to lead to provider regulator capture if the MRA becomes over dependent on fees. Also, the pharmaceutical industry was mentioned as one of the sources of 'other funding. The pharmaceutical industry may fund MRAs as part of its corporate responsibility; however this should be done in the most transparent manner.

5.3 Marketing authorization (MA)

The WHO recommends the formulation of legal provisions under which applications for MA will be submitted to the MRA for assessment based on safety, quality and efficacy (23, 24). All of the 12 reporting countries had legal provisions for premarket evaluation and market authorization (product registration). The study did not specifically investigate the scope of products covered by the MA legislations. In the 2002 ten country study, an official product registration system also existed in all of the countries even though the scope of registration varied from country to country. For example herbal medicines were not covered in some of the 10 countries. For the 2003 level I and II and the 2003 level I studies, the existence of legal provisions on MA was about 134 out of 152 and 135 out of 153 countries respectively. These findings demonstrate a broad existence of regulatory legislation and enforcement of market authorization for medicines. This 2010 pilot study was not able to measure whether the situation has changed since 2007, but when the

country profile global activity takes place in 2011, this will be possible.

It is also worth noting that the public availability of the list of registered products was not as common as the existence of legal provisions on MA among the pilot study countries. This observation reinforces a similar finding in the 2007 level 1 survey where the list of registered products was available in only 106 out of 153 study countries. Public access to the list of registered products is essential in promoting the rational use of medicines.

All of the twelve pilot study countries had legal provisions requiring the registration of medicines by INN name. The INN system, which was initiated in 1950 by the WHA aims at providing health professionals with a unique and universally available designated name for each medicine (26). The INN system is to enhance clear identification, safe prescribing and dispensing of medicines to patients and to make communication and exchange of information among the stakeholders in health care delivery easier. As the approval of market authorization marks the entry point of a pharmaceutical product onto the market, the registration of products by the INN name is very important in the nomenclature of pharmaceuticals. During the 2007 level I and II survey of 89 out of 108 countries used INN in the registration of medicines.

The timeline for the registration of medicines should be long enough to enable the MRA to thoroughly evaluate the safety and efficacy of the product but short enough to ensure that the medicine gets to the patients who need it in time. Though official registration timeline varied from 3 months (Nigeria) to 14 months (China), this may not be the case in practice in the study countries. The real timeline for the registration of products could also be affected by the resources available in the country as well also type of pharmaceutical under consideration (for example whether the product is an NCE or a generic). This pilot study did not evaluate the actual registration time for NCEs and generic products separately. The 2002 ten country study found a difference in the actual registration times for NCEs and generics in four countries. It also identified the existence of fast-track application processes with shorter registration timelines in eight of the countries. Such information could be collected in future country profile studies.

The average ratio of NCE to generic product registration fees of 3 indicates the promotion of generic products through MA in the study countries. Some countries had different fees while others had the same for registering NCEs and generic products. However, the amount charged for generics varied from $18 to $ 8,000. Such higher fees may prevent access to lower cost generic equivalents.

5.4 Regulatory Inspection

The existence of legal provisions on regulatory inspection could be described as satisfactory. Eleven out of the twelve countries had legal provisions for the appointment of government pharmaceutical inspectors. Legalisation of the appointment of inspectors is necessary to provide the legal support to their activities. All of the respondents in the 2002 ten country study indicated the existence of laws requiring both GMP inspection and the inspection of distribution channels. The 2007 level I survey showed that 138 out of 151 countries had legal provisions for the inspection of pharmaceutical premises. Both the 2002 and 2007 studies also looked at the existence of Standard Operating Procedures for GMP inspectors and distribution channel inspections. While legal provisions are paramount, administrative provisions such as SOPs are also important in ensuring compliance with the law. The next pharmaceutical country profile survey could therefore look at the existence of SOPs for inspections as well as national legislations. The WHO has established guidelines for inspectorates of drug distribution channels which among other issues discuss the qualification of inspectors and the inspection methods (27).

5.5 Import Control

In general, legal provisions governing the importation of pharmaceuticals existed in the study countries. Import control is important since every country relies on the importation to meet its pharmaceutical needs. The MRAs in the 2002 ten country study all had import control as part of their regulatory functions. According to the WHO guidelines on the import procedures for pharmaceutical products which were developed in consultation with national drug regulatory authorities, the pharmaceutical industry, the World Customs Organization and the United Nations International Drug Control Program, the importation of pharmaceutical products should be done in conformity with regulations enforced by the national drug regulatory authority (28). Also, all transactions relating to importation of pharmaceutical products should be conducted through a government drug procurement agency or through wholesale dealers specifically designated and licensed by the national drug regulatory authority for this purpose. These guidelines place the responsibility of import regulation on the individual countries involved. However, Nigeria did not report having any legal provision on the importation of pharmaceuticals though this does not imply there are no administrative platforms for importing medicines into the country.

5.6 Licensing

The existence of legal provisions for the licensing of pharmaceutical manufacturers and distributors (wholesalers and retailers) existed in all of the countries. The difference between conformity to the WHO guidelines for manufacturing and distribution was in the level of existence of Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP) in the study countries. While legal provisions requiring compliance with GMP existed in nearly all of the countries, only half of the study countries had legal provisions requiring compliance with GDP. The 2002 ten country study also concluded that in many of the countries, the regulation of manufacturing receives more attention and resources than the regulation of distribution. The ultimate aim of GMP, which is to produce medicines with the highest standard of quality and safety would be defeated if GDP is not given the same attention to be ensure the product gets to the consumer through a distribution system that maintains its quality.

The 2002 report on the World Medicines Situation, the 2003 level I and II survey and the 2007 level II surveys indicated comparable rates of inspection of manufacturers and distribution channels. However these studies did not compare legislation requirements of GMP and GDP in the countries. The implication could be that inspection of distribution channels were carried out without the necessary legal requirements on GDP for both distribution channel inspectors and distributors and retailers to follow.

Legal provisions requiring the publication Good Pharmacy Practice Guidelines (GPPG) as well as those requiring the publication of a list of the different categories of pharmaceutical facilities, was comparatively less common in the study countries compared to the existence of other legal provisions on licensing. The relatively low existence of these provisions does not necessarily mean that GPPG and the list of pharmaceutical facilities are not published in the countries. However the presence of a legal support for these publications is likely to make MRA consistent in publishing them.

5.7 Market Control and Quality Control

Legal provisions for market control existed in 10 out of the 11 responding countries. The pharmaceutical market is characterized by high level of asymmetry of information among the various stakeholders - manufacturers, wholesalers and retailers, health care providers and consumers - on drug efficacy, quality, appropriateness etc (30). In addition to possible failure of competition and 'externalities' the pharmaceutical market is prone to failure and therefore countries need to have legislations on market control. Since the pharmaceutical market is not a perfect market, it must be regulated (29).

All of the pilot study countries had quality control laboratories and also collected and tested samples as part of post marketing surveillance. However, only two (Austria and China) out of the ten countries made their testing results publicly available. This failure to report on testing results in eight out of ten countries does not promote public accountability and transparency in the management of testing of results and the quality of pharmaceutical products on the market.

The increase in the number of samples taken for testing with the number of pharmaceuticals registered in the countries indicates increased post marketing surveillance activity with the number of products on the market. This assumption should however be made with caution because the increase in the number of products taken for testing does not mean an increase in the different types of products. The failure rate of samples at testing also varied from 1% in Suriname (2 out of 370) and Jordan (176 out of 16,049) to 39% (7 out of 18) in Armenia. Since a higher failure rate may mean a stringent quality control system, targeted sampling and testing or poor compliance to GMP, the interpretation of this result should be done in combination with other country specific situations like GMP compliance, as well as the source of the failed products. The WHO guiding principles for small drug regulatory authorities recommends the sampling and analysis of finished medicinal products released into distribution chain to ensure their compliance with working labels (18).

For the 2002 ten country study, all the countries had legal provisions requiring product analysis as well as laboratories for quality control. None of the ten countries contracted pharmaceutical quality control services outside the countries. The failure rate of samples at testing ranged from 1.4% to 23.8%. The results of the 2007 level I study showed that quality management systems were in place in 103 out of 141 countries while post marketing pharmacovigilance activities took place in 104 out of 138 countries. These figures show the general actions by countries to control the quality of pharmaceutical products.

5.8 Medicines advertising and promotion

Legal provisions on advertising and promotion: All of the 12 countries in the 2010 pilot study had legal provisions controlling advertising and promotion of medicines. For the 2002 ten country study, legal provisions on medicines and advertising existed in all the countries. The 2003 level I study showed that 133 of the 128 countries had policies on the promotion and advertising of medicines. The 2002 World Medicines Situation report showed 109 countries out of 192 had laws on the promotion and advertisement of

medicines. These statistics indicate a wide presence of legislations on medicines advertising and promotion over the years. The WHO has published criteria for medicinal drug promotion with the aim of improving healthcare through rational drug use (31).

Code of conducts on promotion and advertising: Compared to legislations on advertising and promotion, codes of conduct were less common in the study countries. Only eight out of twelve respondents had national code of conducts. Also adherence to the code is voluntary in half of the countries that had codes. The other concerns included the limited number of countries with formal processes for complaints and sanctions in their codes of conduct (only five) and the poor publicity given to sanctions imposed. These responses did not indicate the effective use of the codes of conduct in the study countries.

4.9 Clinical Trials

Compared to the existence of legal provisions on other regulatory functions, the existence of legal provisions regulating clinical trials was less frequent in the twelve 2010 pilot study countries. The provisions on the survey instrument that were least complied with by the countries were the existence of legal provisions requiring the compliance of investigational products with GMP compliance (four out of nine countries), legal provisions that require the sponsor and investigator to comply with good clinical practice (six out of nine countries) and legal provisions requiring the registration of clinical trials into international, national regional and registries (six out of eight countries). Another short fall in the regulation of clinical trials is the publication of Good Clinical Practice Guidelines which took place in only four out of the nine countries. The provisions controlling the regulation of clinical trials in the different ten countries involved in the 2002 study were more comprehensive than the current study.

4.10 Controlled substances

All of the study countries are signatories to the international conventions on controlled substances. National laws and regulations and regulations for the control of narcotic and psychotropic substances and their precursors also existed in all the twelve 2010 pilot study countries. However, only four countries confirmed having their laws reviewed by a WHO or any partner organization to evaluate the balance between the prevention of abuse and demand for medical need. The WHO has identified the lack of access to medicines controlled under international drug treaties and have therefore introduced the Access to Controlled Medicines Program (32, 33). The program aims to improve access to controlled medications through a number of interventions which includes policy analysis and review of legislation to identify possible means of improving access (32-35).

In the 2007 level I survey, all the 152 respondents were signatories to international conventions on the control of narcotics and legal provisions for the control of narcotics existed in 150 out of 154 countries. This shows that the existence of legal provisions on narcotics is widespread among WHO member countries.

4.11 Pharmacovigilance

Legal provisions on pharmacovigilance: The first systemic international efforts were initiated to address drug safety issues after the 1961 thalidomide disaster (36). Pharmacovigilance began with a WHO Pilot Research Project for International Drug Monitoring in 1968. Systems were later developed in WHO Member States for the collection and evaluation of case histories of ADRs. The aims of pharmacoviglance include; improving patient care and safety, assess the benefit harm effectiveness and risk of medicines, promoting education and training in pharmacovigilance and its effective communication to the public.

The strengths in pharmacovigilance identified in the study countries included the existence of pharmacovigilance centres that are linked to the MRAs (10 out of the 11 countries), the use of official standard forms for ADR reporting, the provision of feedback to ADR reporters, and the computerization of ADR databases, the submission of ADR reports to the database of the WHO and the organization of training courses pharmacovigilance in the study countries. These structures and systems are important in in ensuing the success of pharmacovigilance activities and are recommended by the WHO (36, 37, 38).

Though the above systems exist in most of the study countries, the legislations in support of these activities are less frequent. For example, legal provisions for pharmacovigilance activities existed in only five out of nine responding countries. Considering the probably differing interests of stakeholders concerned with ADRs and the possible devastating consequences of ADRs, it is important to base pharmacovigilance activities on legislations (39, 40). According to the results of the 2002 ten country study, ADR monitoring systems existed in nine out of the 10 countries. The 2003 level I survey showed that ADRs were monitored in 67 out of 128 countries. The results of the 2007 level 1 survey showed an ADR monitoring systems in 104 out of 155 countries which represents an increase in the proportion of countries monitoring ADR from the 2003 level I survey.

Reporting of ADRs: The stakeholders identified by the WHO working in pharmacovigilance includes national pharmacovigilance centres, hospitals and academia, health professionals, patients and other partners including the media and advocacy groups (36,37,41). One of the important duties of these stakeholders is reporting ADRs. Health professionals reported ADRs in all of the ten respondent countries. However, consumer reporting of ADRs took place in only four of the ten reporting countries. The possible barriers to consumer reporting include; physician biased reporting systems, the lack of knowledge of consumers on drugs and ADRs, poor labelling and identification of dispensed medications and the treatment of internet reporting as anecdotal (41). Nonetheless consumer reporting has the following advantages: early detection of ADRs, complete description of ADRs that otherwise would be unlikely to be clear to the prescriber, and the provision of information that is not normally available to existing systems. Overreliance on pharmacist and physician reporting of ADRs is likely to misidentify or completely miss vital ADRs.

Nine of the countries had records of ADR reports in their database, with China having the highest (638,996). Eight countries have reported ADRs to the WHO ADR Monitoring Centre in Uppsala within 2 years prior to the survey. The Uppsala Monitoring Centre manages the international database of ADR reports received from national pharmacovigilance centres which have electronic access to this database (36). All ADRs from national pharmacovigilance centres are supposed to be reported to the Uppsala Monitoring Centre. However, only Kenya, Nigeria and Suriname reported all their ADRs to the centre. According to the 2002 ten country study results, nine out of the ten countries reported ADRs to the WHO while in the 2007 level I survey, 76 out of 143 reported ADRs internationally.

6.0 Conclusions

Based on the results of the 2010 pilot study, the following conclusions could be drawn on the pharmaceutical regulatory systems of the twelve study countries:

i) Generally, legal provisions exist that establish the regulatory framework of MRAs in the study countries. Legal provisions on marketing authorization, regulatory inspection, import control, licensing, market control and quality control, medicines advertising and promotion, and controlled substances were common and comprehensive in all of the study countries.

ii) Legal provisions regulating clinical trials and pharmacovigilance were less common in the pilot countries.

iii) Assessments of national regulatory systems within five years prior to the study were undertaken in only seven out of the ten countries.

iv) Out of the twelve countries, eight regulatory agencies were funded by government budgets, seven by fees from user services and eight by funds from other sources which were mainly donors. None of the countries were funded by user fees alone and China was the only country in which the MRA relied solely on the government budget.

v) While only nine of the MRAs in the study countries owned websites, this can be regarded as a positive development considering the findings of earlier studies and the fact that the use of websites is relatively new to pharmaceutical regulation.

vi) Legal requirements that MRAs be transparent in the execution of their mandate were less common. Examples of these provisions include: Legal provisions requiring the declaration of potential conflict of interest for experts involved in the assessment and decision making for registration and the publication of summary product characteristics of registered medicines. Furthermore, the publication of a list of different categories of pharmaceutical facilities and products, the publication of quality testing results, the publication of GMP, GDP and GCP requirements and the publication of the list of complaints and sanctions concerning violation of codes of conducts were rarely done in the pilot countries.

vii) The application fee for the registration of New Chemical Entities and the registration of generic products were the same in three countries, while the former was higher in five other countries. The average ratio of the registration fee for NCE to generic of 3 appears to be too low and does not reflect the promotion of generic products.

viii) Legal provisions on Good Manufacturing Practice were more comprehensive and more common than legal provisions on Good Distribution Practice in the countries.

ix) Though pharmacovigilance activities widely existed in the study countries, legal provisions backing these activities were less common.

x) While health professionals reported ADRs in all the study countries, consumer reporting was poor. Consumers reported ADRs in only four countries.

Final comments: Since 1999, a number of studies have been undertaken on national pharmaceutical regulatory systems. These have either been global level I and II surveys in 1999, 2003, and 2007 and the World Medicine Situation report in 2002 or the in-depth 2002 ten country study and this 12 country pilot study undertaken in 2010. All of these studies demonstrate variable progress across technical areas. Many more countries have regulatory agency websites, GMP requirements, GDP standards etc. While much remains to be done, progress is occurring.

7.0 Recommendations

The following recommendations are offered in order to improve the 2011 global pharmaceutical profile study. These recommendations concern the regulation section of the instrument as well as other sections from which information was extracted.

i) Soliciting for the total number of licensed pharmacies (as in section 2.02.10) alone may not give a true picture of the pharmaceutical care providers in the study countries. Apart from licensed pharmacies, licensed chemical stores, or other similar facilities which are also regulated exist in some countries. Knowing the number of these facilities will give a good indication of the total number of pharmaceutical care providers in the countries.

ii) The definition for 'inspectors' in section 4.03.02.01 could be more specific and should not include regulatory staffs who work in the laboratory or staff that perform other regulatory duties apart from inspection.

iii) The current definitions for an MRA being part of the MOH or semi-autonomous could make an MRA classifiable into both groups, as could be seen from the study results. The definitions of these two groups should therefore be streamlined.

iv) Section 4.07.06.01 aims to find out whether the code of conducts on advertising and promotion applies to domestic manufacturers, multinational manufacturers or both. Pharmaceutical wholesalers could also be listed as one of institutions to which the code of conduct could apply. Also, the possible answers provided for this section on the survey instrument should be the list of these institutions rather than a ‘yes’ or ‘no’ option.

v) The time limit for the registration of products sought in section 4.02.16 could further be clarified in terms of whether it is the actual time it takes to register a product or whether it is the supposed time. The time it takes to register an NCE and a generic could also be separated.

vi). Apart from the investigation of legal provisions for promotion of advertisement of pharmaceutical products, the existence of legal provisions on regulating the promotion and advertisement of pharmaceutical premises (pharmacies and licensed chemical shops) could also be investigated.

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9.0 Annexes

Annex 1 - Websites of Drug Regulatory Agencies

Country	**Website address**
Argentina	www.anmat.gov.ar
Armenia	www.pharm.am
Austria	http://www.basg.at/bundesamt-fuer-sicherheit-im-gesundheitswesen-basg
China	www.sda.gov.cn
Jordan	www.jfda.jo/EN/default/
Kenya	www.pharmacyboardkenya.org
Maldives	www.health.gov.mv.
Nigeria	www.nafdac.gov.ng
Pakistan	www.dcomoh.gov.pk
Sudan	www.nmpb.gov.sd

Annex II, Urls for lists of registered products

Country	**URL**
Argentina	www.anmat.gov.ar
Armenia	http://www.pharm.am/jurdocs_list2.php?pg=13&id=10&langid=2
Austria	http://pharmaweb.ages.at/pharma_web/index.jsf
Maldives	http://www.health.gov.mv/ Look under Standards for information on: Approved Drug List
Nigeria	www.nafdac.ng.gov.
Sudan	www.nmpb.gov.sd
Suriname	not available on internet - List is available upon request from Registration Bureau

Annex III Codes of conducts for advertising and promotion.

Country	Document on code of conduct
Austria	The Association of the Austrian Pharmaceutical Industry, Code of conduct Reprozwolf Spannbauer Ges. mbH and CoKG, Vienna, 2009
Nigeria	Registration and regulatory affairs directorate, guidelines for the advertisement of regulated products in Nigeria NAFDAC/RR/091/00
Pakistan	Drug Act, 1976, Advertising of drugs

Annex IV, Narcotic laws review documents

Country	Link to document or document name
Armenia	www.scadarmenia.org
Pakistan	National AntiNarcotic Policy of Pakistan
Sri Lanka	www.nddcb.gov.lk
Suriname	www.cicad.oas.org/MEM/ENG/Reports/Fourth%20Round%20Full/Suriname%20-%20Fourth%20Round%20-%20ENG.pdf