WHO-EM/EDB/043/E

Developing regional guidelines on minimum requirements for the registration of herbal medicinal products

Report of a workshop
Abu Dhabi, United Arab Emirates
7–9 June 2003

1

World Health Organization
Regional Office for the Eastern Mediterranean
Cairo
2004

Printed by

Document WHO-EM/EDB/043/E/10.04/52

Contents

1. Background 5

2. Introduction 5

3. Technical presentations 6
   - 3.1 Regional overview: the current situation and challenges facing countries of the Eastern Mediterranean Region 6
   - 3.2 Global and national review of the regulatory status of herbal medicine 7

4. Country presentations 7
   - 4.1 Bahrain 7
   - 4.2 Jordan 7
   - 4.3 Qatar 7
   - 4.4 Saudi Arabia 8
   - 4.5 United Arab Emirates 8
   - 4.6 Yemen 8

5. Use and Regulation of Herbal Medicine in Europe: Global Survey on National Traditional/complementary/alternative medicine policy and Regulation of Herbal Medicines 8

6. Working Sessions 9
   - 6.1 Assessing safety and efficacy of herbal medicine 9
   - 6.2 Safety monitoring 11

7. Plenary discussion 12

8. Recommendations 12

Annexes

1. AGENDA 13
2. PROGRAMME 14
3. LIST OF PARTICIPANTS 16
4. THE MINIMUM REQUIREMENTS FOR THE REGISTRATION OF HERBAL MEDICINAL PRODUCTS ..... **ERROR! BOOKMARK NOT DEFINED.**

1. Background

Use of herbal medicines has steadily increased in countries of the WHO Eastern Mediterranean Region. In some countries of the Region, herbal medicines are produced locally and a large population depends on them for primary health care, but in other countries the majority of herbal products are obtained from the United States, Europe or Asia. A major problem in the evaluation of imported herbal products is that many products contain more than 10 plants and it is very difficult to conduct testing and quality control. Another problem is the fact that classificatory categories for herbal products vary from country to country; some categories include functioning foods, dietary supplements and traditional herbal medicines.

Governments need to establish their national regulations on the control of imported herbal medicines through sharing experiences and harmonizing standards on safety and quality control across national boundaries. Previous Eastern Mediterranean Drug Regulatory Authorities Conferences (EMDRAC) in 1999 and 2001 provided general guidance to drug regulatory authorities in the development and implementation of preliminary regulatory systems for herbal medicines. Specific guidance is needed, however, to meet the needs of both countries that are primarily producers and those that are primarily importers of herbal medicines. In 2002, the Forty-ninth Session of the WHO Regional Committee for the Eastern Mediterranean adopted a resolution on traditional medicine (EM/RC49/R.9) in which it requested the Regional Director to take necessary action to develop guidelines for the preparation of national policies and regulations on traditional/complementary/alternative medicine.

In order to develop the regional guidelines on the regulation of herbal medicines, WHO organized two regional workshops on the regulation of herbal medicines for national drug authorities. The first workshop took place in Teheran, Islamic Republic of Iran, from 14 to 17 December 2002. A total of 18 national drug authorities from 8 countries (Afghanistan, Egypt, Islamic Republic of Iran, Morocco, Pakistan, Syrian Arab Republic, Sudan and United Arab Emirates), most of which were producers of herbal medicines, attended the workshop. The workshop focused on controlling the safety, quality and efficacy of local herbal products, and developed draft regional guidelines on how to regulate and control local herbal medicines. The workshop strongly recommended that WHO organize a second regional workshop to review and discuss the draft guidelines developed by the first workshop, focusing on quality control of herbal medicines imported from other countries.

2. Introduction

The second regional workshop on developing regional guidelines on minimum requirements for the registration of herbal medicines was held in Abu Dhabi, United Arab Emirates, from 7 to 9 June 2003, to finalize regional guidelines on the registration of herbal medicines with the main emphasis on quality, safety and efficacy. The workshop was attended by a total of 17 participants from 6 countries of the Eastern Mediterranean Region, Bahrain, Jordan, Qatar, Saudi Arabia, United Arab Emirates and Yemen, most of whom are importers of herbal medicines.

During the inaugural session Mr Mohamed Bin Shahna, Technical Officer, Essential Drugs and Biologicals, WHO/EMRO, delivered a message from Dr Hussein A. Gezairy, WHO Regional Director for the Eastern Mediterranean. In his message, Dr Gezairy thanked the Ministry of Health and noted that the United Arab Emirates had been chosen as the venue for the workshop because it had a long history in the use of traditional medicines, which was also reflected in the establishment of the Sheikh Zayed Complex for Herbal Research and Traditional Medicine.

Dr Gezairy emphasized that traditional medicine was and would continue to be an important component of health care provision around the globe and in the Region. As much as 80% of rural

people in the Region relied on traditional medicine. The use of herbal medicine was increasing, as in the Islamic Republic of Iran, where sales of herbal medicines increased from US$ 3 million in 1999 to US$ 3.5 million in 2001. In many countries, especially those of the Gulf Cooperation Council, herbal products were imported from other countries and therefore the evaluation of safety, quality and efficacy was essential. In some countries herbal medicine and food were in the same category, hence regulation and quality standards of herbal medicine were important. In 2002, he noted, the Forty-ninth session of the Regional Committee for the Eastern Mediterranean had adopted resolution EM/RC49.R9, which urged Member States to develop and implement national policies and regulations on traditional and complementary medicines, to ensure not only that they were used appropriately, but also optimally, as a means of increasing access to primary health care. The resolution had also requested the Regional Office to take the necessary action to develop guidelines on the preparation of national policies and regulations concerning traditional and complementary medicines.

A message from Dr Hamad Abdel Rahman Al Madfaa, Minister of Health, United Arab Emirates, was read by Dr Abdul Ghaffar Abdul Ghaffour, Assistant Undersecretary for Curative Medicine. In his message Dr Al Madfaa welcomed the participants and stressed that the Ministry of Health was seriously following up all the factors that guarantee the quality safety and efficacy of herbal medicines. He also emphasized the growing need to protect and preserve traditional medicine knowledge and natural resources.

Mr Bin Shahna then briefed the participants on the agenda and methodology of the workshop. During the workshop, experts from countries that are primarily importers of herbal medicines would share experiences in the development and implementation of national regulatory policies, within and outside the Region. The workshop participants would review the draft regional guidelines for the registration of herbal medicines to address specific regional requirements, based on existing WHO guidelines and the issues raised during the workshop.

Dr Abdul Ghaffar Abdul Ghaffour, (United Arab Emirates) and Dr Abdullah Al Bedah (Saudi Arabia) were elected as Chairmen of the workshop. Dr Ahmad Ali Al Nomani (Yemen) and Dr Waleed R. Marji (Jordan) served as rapporteurs. The agenda, programme and list of participants of the workshop are included as Annexes 1, 2 and 3. Minimum requirements for the registration of herbal medicines, finalized during the workshop, are attached in Annex 4.

3. Technical presentations

3.1 Regional overview: the current situation and challenges facing countries of the Eastern Mediterranean Region

Mr Mohamed Bin Shahna, Technical Officer, Essential Drugs and Biologicals, WHO/EMRO

The global, regional and national sales of herbal medicines have shown rapid growth during the last decade. According to the Secretariat of the Convention on Biological Diversity (CBD) report, the global medicines market in 2000 was estimated at US$ 60 000 million. In Japan, the herbal medicines market was worth US$ 1000 million in 1991, US$ 2000 million in 1994, US$ 2200 million in 1996 and US$ 2400 million in 2000. In the United Kingdom, this market was worth US$ 92 million in 1994, US$ 134 million in 1998, and US$ 159 million in 2000 and it was expected to reach US$184 million in 2002. For the United States, the figures are US$ 1600 million in 1994, US$ 3000 million in 1997, US$ 4400 million in 1999 and US$ 5400 million in 2000.

In Member States of the Eastern Mediterranean Region, use of herbal medicines also shows a steady increase. For example, according to the estimate of the Ministry of Health and Medical Education of the Islamic Republic of Iran, annual sales of herbal medicines were US$ 3 million in 1999. This

number increased to US$ 3.1 million in 2002 and 3.5 million in 2001. In Pakistan, the sales of herbal medicines reached US$ 52 million in 1999, and were up to US$ 63 million in 2000 and US$ 70 million in 2001. In 2002 the United Arab Emirates imported 2500 tablets, 699 100 capsules and 6100 bottles of herbal medicine; corresponding figures for 2001 were 257 500 tablets, 2 454 160 capsules and 10 122 bottles. The total number of items of imported herbal medicine increased by 385% between 2000 and 2001.

One of the challenges in many Eastern Mediterranean Region countries, particularly in the countries of the Gulf Cooperation Council, is that the majority of herbal products are imported from the United States and European and Asian countries. A major problem in the evaluation of imported herbal products is that many products contain more than 10 plant parts and therefore it is difficult to conduct testing and quality control on these products. Many national authorities have not yet developed the knowledge and technical skill for evaluation of the quality, safety, and efficacy of the majority of herbal products imported into their countries. Classification for herbal products varies from country to country; in some countries traditional herbal medicines are included in the same category as food and dietary supplements.

Overall, there is a lack of cooperation and information-sharing regarding market control between the ministries of health of different countries of the Region. Important data related to safety, efficacy and quality control are often either insufficient or not available. In most countries, either no safety monitoring system exists or the existing system excludes herbal medicines.

3.2 Global and national review of the regulatory status of herbal medicine

Dr Xiaorui Zhang, Essential Drugs and Medicines Policy, WHO/HQ

Dr Zhang presented the situation on the use of herbal medicines, national policy, regulation, registration of herbal medicines, quality control and good manufacturing practices (GMP), national pharmacopoeia and safety monitoring in the Region, based on information from the Global Survey forms received from 10 countries of the Eastern Mediterranean Region.

4. Country presentations

4.1 Bahrain

Medicines derived from herbal, animal and mineral sources and the accepted topical preparations were described. The documents to be submitted for the registration of a health product were explained and labelling was discussed. Additional requirements, such as the content of herbal product and maximum number of herbal components were described. The general rules were also described in detail; the licences to import and sell health products, for example, are given to pharmacies and special outlets. Annual fees and renewal of product licences were also discussed in detail.

4.2 Jordan

The main features described were harmonizing with WHO guidelines on herbal medicine and the formation of a committee for market authorization. The legal status of herbal preparations was classified into three groups: 1) herbs with local knowledge and traditional use; 2) herbs with international knowledge and traditional use; and 3) herbs without the support of international experience. The requirements for these three groups were discussed further. The total programme up to market authorization was shown in a flow diagram.

4.3 Qatar

The first laws and regulations for medicinal plants were formulated in 1983, followed by laws in 1986 and 2002. Functions and tasks of the Professional Committee of Herbal Medicine and Complementary

Products were described. The establishment of the Herbal Medicines, Food Preparations and Cosmetics Sections and their functions and tasks were also described. The main contents of new regulation for registration of herbal medicine, dietary supplements and cosmetics were discussed. Six useful examples of the regulations for TM/HM/CAM in Qatar were given.

4.4 Saudi Arabia

This presentation comprised a briefing on the current situation of the practice of traditional medicine (TRM) and complementary and alternative medicine (CAM), the availability of two kinds of herbal products, from local and imported crude medicinal plants, and the history of traditional medicine in Saudi Arabian culture. The formation of a registration committee for imported and locally produced herbal medicines at the Ministry of Health was discussed.

4.5 United Arab Emirates

There is a long history of the use of traditional medicine. This is reflected in the establishment of the Sheikh Zayed Complex for Herbal Research and Traditional Medicine as an acknowledged centre in this important area, which after many years is seeing a well deserved revival, both regionally and globally. Traditional, complementary and alternative medicine (TCAM) is regulated in the United Arab Emirates jointly by two departments at the Ministry of Health. The Drug Control Department regulates the registration of non-conventional medicines such as herbal, homeopathic, ayurvedic and Chinese medicine, as well as natural products drugstores and pharmacies, while the Complementary and Alternative Medicine Unit coordinates the licensing and regulation of TCAM practitioners. About 53 herbal medicines are registered and another 120 are under the registration process. Approximately 112 traditional, complementary and alternative medicine practitioners including homeopaths, herbalists, acupuncturists, chiropractors and chiropodists, have passed the TCAM qualifying examinations that are held four times a year.

4.6 Yemen

Traditional medicine was described, including herbal medicines, honey and herbal materials and traditional medical practices. Regulations of the Supreme Board of Drugs and Medical Appliances were also described, along with ongoing activities such as the essential herbal medicine list and data collection.

Seventy-five herbal products have been classified and 59 herbal products have been authorized. Regional harmonization of regulations is needed, along with a standardized list of categories, access to international literature and databases, and qualified ministry of health staff with international experience.

5. Use and regulation of herbal medicine in Europe: Global survey on national traditional/ complementary/ alternative medicine policy and regulation of herbal medicines

Out of 40 countries in the WHO European Region, survey forms were received from Austria, Bulgaria, Denmark, Estonia, Hungary, Kyrgyzstan, Latvia, Netherlands, Portugal, Switzerland, Turkmenistan and Uzbekistan. Results of the survey show increasing use of herbal medicines in the European Region, with some countries having a national policy with regard to traditional medicine, e.g. Hungary and Ukraine. Countries intending to establish a national policy of traditional medicine are Armenia, Bulgaria, Czech Republic, Israel, Slovenia and Uzbekistan.

Countries with national office or expert committee and countries with regulations for traditional medicine in the European Region are Armenia, Austria, Bulgaria, Czech Republic, Denmark, Estonia,

Germany, Hungary, Israel, Kyrgyzstan, Latvia, Netherlands, Portugal, Slovenia, Switzerland, Turkmenistan, Ukraine and Uzbekistan.

Countries using GMP for quality control in herbal medicine products are: Armenia, Austria, Bulgaria, Czech Republic, Denmark, Estonia, Germany, Hungary, Israel, Latvia, Netherlands, Portugal, Slovenia, Switzerland, Turkmenistan, Ukraine and Uzbekistan.

Countries with their own national safety monitoring system for herbal medicines are: Armenia, Austria**,** Bulgaria, Czech Republic, Denmark, Estonia, Germany, Hungary, Israel, Netherlands, Portugal, Slovenia, Switzerland, Turkmenistan and Ukraine. Concluding the talk it was stated that the only country intending to establish a monitoring system is Kyrgyzstan.

6. Working Sessions

6.1 Assessing safety and efficacy of herbal medicine

A round-table discussion was held on the safety and efficacy of herbal medicine under the chairmanship of Dr Abdullah Al Bedah. The major challenges discussed were on how to assess the safety and efficacy of the herbal products, whether the information provided by the manufacturer should be trusted, and what studies are being performed by the regulatory authorities to check the validity of the documents provided by the suppliers. The different guidelines for safety and efficacy of single and complex medicine were discussed in detail. Different factors involved, e.g. lack of money, interest, facilities, methodology, evidence, etc. were considered. Safety is more important than efficacy but since there is no harmonization, guidelines are required for safety and efficacy.

Dr Xiaorui Zhang outlined the major differences between traditional herbal medicines and conventional medicines affecting their regulation; in particular the major difficulties and challenges for evaluating safety and efficacy for the former. She introduced the WHO technical guidelines on safety and efficacy evaluation. Regulatory authorities have to control safety and efficacy of traditional medicines, but the characteristics and theory of traditional medicine need to be taken into consideration when developing approaches and methods for the evaluation and regulation of herbal medicines. She also summarized the requirements for safety and efficacy in the draft regional guidelines developed by the first regional workshop in 2002.

Mr Raymond Tsang proposed the Canadian System for Assessment of Safety and Efficacy of Natural Health Products and covered the following points in detail:

- standards of evidence
- standing committee on health recommendations on standards of evidence
- categorization of ingredients
- traditional use
- previous marketing experience
- National Health Products monographs
- new ingredients
- safety summary report
- identifying safety issues:
- literature review
- toxicity testing
- combination products.

He concluded his talk by emphasizing that this system provides substantial flexibility for industry, ensures consumers ready access, enhances consumer and practitioner confidence and promotes international harmonization.

Dr Mohammed Tariq Rida discussed traditional medicine, complementary and alternative medicine, challenges, WHO's role, and Eastern Mediterranean Drug Regulatory Authorities Conferences (EMDRAC), two sessions of which on regulation of herbal medicines held in 1999 and 2001 provided guidance for the development and implementation of preliminary regulatory systems and national policy programmes. He discussed the great challenges facing countries in the areas of regulations and national policies, and technical knowledge and capacity. He also discussed the challenges for safety, efficacy, quality and post-marketing monitoring of herbal medicines. The solution to meet the challenges was regional harmonization in regulations and policy on herbal medicines. Suggestions were to introduce a series of WHO documents related to herbal medicines; share data and information on the regulatory situation of herbal medicines; facilitate the dissemination of documents, guidelines and other materials and expertise between countries of the Region; and develop, based on available WHO technical guidelines, country-specific materials at national level.

Two working groups were formed, Group One to discuss safety issues and Group Two to discuss efficacy, in combination with relevant sections from the draft regional guidelines on the regulation of herbal medicines from the first regional workshop.

Group One discussed major challenges and minimum requirements on safety of imported herbal products. Corrections were made for category of disease, preclinical and clinical data of efficacy wherever needed.

Group Two discussed major challenges on minimum requirements on safety of imported raw material and products. Well established safety data for different categories, method of preparation, mode of administration and toxic city studies were discussed and changes were made.

The changes made in the two groups for safety and efficacy were discussed by all the delegates together and the draft was finalized. The major challenges in quality control studies on imported raw material and herbal products were discussed in detail including the organoleptic factors, identification, and assay. It was pointed out that information and appropriate standards can be found in official pharmacopoeias, monographs and handbooks. WHO guidelines on quality control should be followed. In case a full validation of more sophisticated methods such as high performance liquid chromatography, gas chromatography and gas chromatography/mass spectrometry is not possible, it may be preferable to use simple methods such as microscopic identification, thin layer chromatography, titration etc. The parameters required for product information were discussed and finalized.

Dr Xiaorui Zhang gave an introduction to WHO guidelines for the requirements of quality control of medicinal products including Good Sourcing Practices (GSP) and Good Manufacturing Practices (GMP) guidelines and activities for quality control. The presentation covered the following topics: minimum requirement for the quality control of herbal medicines such as plant identification, purity testing and quality control methods. Dr Zhang introduced several WHO technical guidelines related to quality control of medicinal materials including good agricultural practice and good field collection practice, good manufacturing practice for herbal medicines, sanitation and hygiene.

She also described the Singapore regulations for quality control of imported herbal medicines. She concluded that quality control of herbal medicines and herbal products is a very complicated issue and should therefore be managed carefully at each and every step of the production process.

Mr Raymond Tsang described the Canadian system for assessment of quality assurance of natural health products. The following outlines were discussed in detail:

- product licensing
- site licensing
- good manufacturing practices
- clinical trials involving human subjects
- packaging and labelling.

Good manufacturing practices are divided into the following categories: places (premises and equipment); people (personnel) and quality products (specifications, stability, samples, records, recall reporting and sterile products). In conclusion Mr Tsang discussed ongoing consultations, publication in Canada Gazette Part II, staged implementation to allow smooth transition, release of accompanying guidance documents, national outreach and education programme.

Following the discussions of the working groups, there was a round-table discussion on quality control, Good Agriculture and Collection Practices (GACP) and GMP. It was agreed that the manufacturer should adhere to GACP and GMP standards and establish appropriate specifications for their products. Further quality assurance is a shared responsibility of manufacturer and health regulatory bodies and hence a cooperative approach is encouraged. National health authorities should establish guidance on quality assurance and check post-marketing compliance with the specifications set out by the producer and GMP compliance. In order to promote implementation of GACP practices, incentives should be offered to producers of raw materials.

6.2 Safety monitoring

The report of the working group on pharmacovigilance of herbal medicinal products was discussed. Pharmacovigilance units are necessary to collect and assess information on herbal and traditional medicine. All countries have contributed their experiences and realized ever though it is a long term policy, it is important. Each herbal medicine must be clearly identified by its composition, brand name and dosage. Adverse drug reaction (ADR) was discussed with all the associated factors and relationships.

Dr Xiaorui Zhang discussed the current WHO global drug safety monitory system and its operating mechanism. Drug safety monitoring is a relatively new area and only 68 Member States have established their own national drug safety monitoring systems which mostly do not include herbal medicines. The WHO guidelines for herbal medicine safety monitoring, which are under development, will help Member States address this gap and will contribute to the promotion of safe use of herbal medicines. Dr Zhang also summarized post-marketing in the draft Eastern Mediterranean regional guidelines and introduced control of advertisements of traditional herbal medicines from the WHO African Region guidelines.

Mr Raymond W. Tsang discussed the proposed imported products safety monitoring system for natural health products. His talk included an outline of the Canadian Food and Drugs Act and Regulations, which can be applied when the inspector believes on reasonable grounds that any provision of this Act or the Regulations has been contravened. He further proposed an imported products safety monitoring system, inspections and investigations, information database, laboratories support, techniques accredited in 2002, techniques which should be accredited in 2003–2004.

Future plans were discussed which include method development and method validation for identification of active ingredients in drugs or natural health products for which validated methods do not exist (support to investigation); screening for toxic compounds, unknowns, undeclared active ingredients, etc.

Mr Tsang also discussed the post-marketing products survey, information exchange, compliance and enforcement and challenges. The concluding suggestions were to reduce the number of unsafe products in the marketplace; provide access to safe, effective and high quality imported products; develop expertise in the process and promote compliance in the process.

7. Plenary discussion

The Chairman invited Dr Zhang to discuss minimum requirements for the safety and quality control for imported herbal medicines in combination with safety and quality control parts in draft regional guidelines on the registration of herbal medicine.

Dr Zhang emphasized that the main aim of WHO is that each region should develop its own regulations and in this way they can cooperate or the safety and quality control of imported herbal medicines in combination with the safety and quality control sections in the draft regional guidelines on the registration of herbal medicines. She stressed that national governments should develop a national programme. WHO is ready to assist if a government develops its national programme on integration of traditional medicine. It is believed that governments should make a commitment to support WHO schemes.

Mr Bin Shahna highlighted the importance of traditional medicines, and noted that in the coming months EMRO would be conducting joint programme review and planning mission (JPRM) exercises with countries for the 2004–2005 biennium, so according to their priorities, countries may wish to have some activities relevant to traditional medicine for the next two years.

8. Recommendations

The participants of the second regional workshop on the registration of herbal medicines expressed support for the recommendations of the first regional workshop on regulation of herbal medicines in Teheran in 2002, emphasizing the importance of the following recommendations:

1. The health authorities should recognize the importance of traditional and complementary/alternative medicine (TM/CAM) in general and herbal medicine in particular, according to the country situation regarding their use.

2. National and regional expert committees on TM/CAM should be established.

3. An official structure for TM/CAM should be set up within ministries of health to coordinate the implementation and monitoring of national policy on TM/CAM.

4. National regulations on herbal medicines should be established or updated.

5. A regional reference centre for TM/CAM should be established to promote research on quality, safety and efficacy of herbal medicines.

6. A national list of medicinal plants should be developed, based on level of safety.

Annex 1

Agenda

1. Opening of the workshop
2. Nomination of Chairperson, Vice-Chairperson, Rapporteur and Group Chairpersons
3. Adoption of the agenda
4. Policy and country presentations
5. To review the draft regional guidelines for herbal medicines
6. Methodology for assessment and evaluation of imported traditional and herbal medicine
7. Quality control for imported traditional medicine and herbal medicine
8. Regulation and safety monitoring
9. Towards common principles and goals in regional regulatory harmonization
10. Recommendations
11. Other items
12. Adoption of the report
13. Closure of workshop

Annex 2

Programme

7 June 2003

08:30–09:00	Registration of participants
09:00–10:30	Opening remarks Welcome address, Ministry of Health Message from Dr Hussein A. Gezairy, WHO Regional Director for the Eastern Mediterranean Nomination of Chairperson, Vice-Chairperson, Rapporteur and Group Chairpersons; Adoption of Agenda Briefing of the workshop (Mr Mohamed Bin Shahna)
Working Session 1: Global and national review of regulatory status of herbal medicine	
10:30–11:00	Situation on the use of herbal medicine and regulations in the Region and summary of results of the Global Survey in countries of the Region (Dr Xiaorui Zhang) Integrating traditional medicine into NDP
11:00–14:00	Country presentations: discussing the successes and challenges (Each country presentation will last 10 minutes)
Working Session 2: Assessing safety and efficacy of herbal medicines	
14:00–15:00	Roundtable discussion of major challenges in assessing safety and efficacy
15:00–17:00	Introduction of WHO guidelines for assessment of safety and efficacy of herbal medicine (Dr Xiaorui Zhang) Introduction of Singapore system for assessment of safety and efficacy of herbal medicines including imported herbal medicines Introduce draft regional guidelines on the registration of herbal medicines from the first regional workshop (Dr Mohamed Tariq Rida)
17:00–18:30	Working group discussions safety and efficacy in combination with safety and efficacy part from draft regional guidelines on the registration of herbal medicines from the first regional workshop Group 1 on major challenge and minimum requirements on safety Group 2 on major challenges and minimum requirements on efficacy

8 June 2003

08:30–09:30	Reports by working groups
Working Session 3: Quality assurance	
09:30–11:00	Roundtable discussion of major challenges in quality control focus on the raw materials and GMP
11:00–12:00	Introduction to WHO GSP and GMP guidelines and activities for quality control (Dr Xiaorui Zhang) Introduction to Singapore system for quality control of imported herbal medicines and European GSP guidelines for quality control
12:00–14:00	Working groups discussions: quality control GACP and GMP in combination with quality control part from draft regional guidelines on the registration of herbal medicines from the first regional workshop Working Group 1 on GMP

	Working Group 2 on GSP and the quality control methods of herbal materials
14:00–15:00	Reports by working groups
Working Session 4: Safety monitoring	
15:00–16:30	Roundtable discussion of major challenges in safety monitoring
16:30–17:30	Introduction to WHO guidelines and activities for monitoring safety of herbal medicines (Dr Xiaorui Zhang)
	Introduction to herbal medicine safety monitoring in Singapore

9 June 2003

08:30–09:30	Working group discussions on safety monitory in combination with quality control part from draft regional guidelines on the registration of herbal medicines from the first regional workshop
	Working Group 1 focus on report system on how to set up or expand safety-monitoring systems
	Working Group 2 focus on methods for analysis of cases of adverse effects
09:30–11:00	Reports by working groups
Working Session 5: Development of common requirements for registration of herbal medicines	
11:00–14:00	Plenary discussion
14:00–16:00	Recommendation
	Adoption of report and recommendations
16:00	Closing remarks

Annex 3

List of participants

BAHRAIN
Mrs Farida Aly Abd El Wahab
Head of Inspection and Pricing, Drug Control Department
Ministry of Health
Manama
email: ipr@health.gov.bh

Mrs Sahar M. Saleh Al Kahtani
Senior Pharmacist
Department of Inspection and Pricing
Ministry of Health
Manama
email: mhealth@batelco.com.bh

CANADA
Mr Raymond W. Tsang
Chief, Compliance and Enforcement Division
Natural Health Products Directorate
Health Products and Food Branch
Ottawa

JORDAN
Dr Waleed Rasmi Marji
Pharmacist
Ministry of Health
Herbal Drug Registration
Amman

Mr Bajes Ahmad Bani Melhem
Pharmacist
Ministry of Health
Irbid

QATAR
Dr Mohamed Bashir Ali
Pharmacist, Drug Control Department
Ministry of Public Health
Doha
Email: bashir771@yahoo.com

Dr Zakiya Ali Malallah
Officer, Unit of Follow-up, Research and Information Centre
Ministry of Public Health

Doha

SAUDI ARABIA
Dr Abdullah Al Bedah
Assistant Director General, Hospitals
Ministry of Health
Riyadh
Email: aalbedah3@yahoo.com

Dr Khaled Abdul Aziz Al Smari
Pharmacist, Registration Department
Secretary, Drugs Registration Committee
Ministry of Health
Riyadh

UNITED ARAB EMIRATES
Dr Abdul Ghaffar Abdul Ghaffour
Assistant Undersecretary for Curative Medicines
Ministry of Health
Dubai
Email: alhawiag@hotmail.com

Dr Eassa Ahmed Bin Jakka Al Mansoori
Director of Drug Control Department
Ministry of Health
Abu Dhabi
Email: Essaj@moh.gov.ae

Dr Mazen Ali Naji
General Director
Sheikh Zayed Complex for Herbal Research and Traditional Medicine
Abu Dhabi
Email: druae@hotmail.com

Ms Fatima Ali Abdulla Al Braiki
Deputy Director of Drug Control Department
Ministry of Health
Abu Dhabi
Email: fabdallah@moh.gov.ae-Drugd@moh.gov.ae

Mr Tariq Rida Osman
Officer In Charge, Herbal Medicine Registration
Drug Control Department
Ministry of Health
Abu Dhabi
tariqm@moh.gov.ae

Dr Sassan Bahjat
Coordinator
Office of Complementary and Alternative Medicine
Ministry of Health
Abu Dhabi
Bahjat@emirates.net.ae

Mr Abdul Hamid Al Humoud
Manager, International Relations
Ministry of Health
Abu Dhabi
Exrel@moh.gov.ae

Mr Mohamed Al Khatib
International Relations Department
Ministry of Health
Abu Dhabi

YEMEN

Dr Ahmed Ali Al Nomani
Director General of Pharmaceutical Services
Ministry of Public Health and Population
Sana'a

Dr Kamal Abdul Fateh Al Shamiri
Focal point for Herbal Medicine
Ministry of Public Health and Population
Sana'a

OBSERVERS

JAPAN

Mr Reizo Utagawa
Executive Director for International Affairs
The Nippon Foundation
Tokyo

Ms Makiko Ogihara
Programme Officer
The Nippon Foundation
Tokyo

JORDAN
Dr Sameer Otoom
Co-Chair, Committee of Herbal Medicines
Jordan University for Science and Technology
Amman

SAUDI ARABIA
Dr Mansour S. Al Said
Dean, College of Pharmacy
King Saud University
Riyadh

Mr Mohamed Saud Al Mutairi
Pharmacist
Ministry of Health
Riyadh

Mr Abdullah Fahad AlMesnad
Pharmacist
Ministry of Health
Riyadh

UNITED ARAB EMIRATES
Ms Asmaa Essa Obied Alzaabi
Ministry of Health
Abu Dhabi

Ms Aline Abi Zeid Daou
In charge of Registration of General Sale Products/Food supplements
Ministry of Health
Abu Dhabi

WHO SECRETARIAT

Dr Xiaorui Zhang, Acting Coordinator, Traditional Medicine, Essential Drugs and Medicines Policy, WHO/HQ
Dr Mohamed Bin Shahna, Technical Officer, Essential Drugs and Biologicals, WHO/EMRO
Ms Heba El Khoudary, Senior Administrative Clerk, WHO/EMRO

Annex 4

Minimum requirements for the registration of herbal medicinal products

Categorization of herbal medicines

Traditional herbal medicines

This is defined as any herbal medicine (single or more herbs and fixed combinations of herbs) that has been widely used, supported by well-established safety data, or used within the local community for a minimum time period of 15 years. This would include herbal medicines that are very similar to such products, e.g. if some ingredients have been eliminated from a traditional fixed combination. Herbal substances that are not indigenous to the Region, e.g. ginseng root, could be included, if the wide use within the Region guarantees sufficient knowledge and safety.

New herbal medicines

Herbal medicines (single or more herbs and fixed combinations of herbs) can be considered "new herbal medicines" if never used within the community, used for only a short period of time, used to a very small extent (few uses in a small number of patients), or used in a new combination of herbal substances never combined before, if without well-established safety data support.

In order to promote a harmonized assessment, a regional list of traditional herbal substances/combination of substances is proposed. This list should originate from proposals submitted by countries to the WHO Regional Office for the Eastern Mediterranean. The list should contain the following items:

- scientific botanical name of the plant (Latin binominal nomenclature)
- common/English name of the plant
- common names of the plant in regional languages
- plant part used
- name of the herbal drug
- common name(s) of the herbal drug
- methods of preparation, e.g. powder, herbal tea, extract with ethanol, distillate
- mode of administration (e.g. oral, external, inhalation)
- range of safe dosages (daily dose) as found in literature
- safety category
  - Category I: no concern related to safety
  - Category II: safe under specific conditions of use (herbal medicines should preferably be covered by well-established documentation)
  - Category III: unsafe herbs.

Requirements for safety of "new herbal medicines"

The required safety data for new herbal medicines will be identical for any new substance:

- single dose toxicity
- repeated dose toxicity
- chronic toxicity
- organ targeted toxicity, if necessary
- immunotoxicity
- embryo/foetal and prenatal toxicity, if necessary
- mutagenicity/genotoxicity, if necessary
- carcinogenicity, if necessary

- local tolerance.

In special circumstances, such as new combinations of well-known substances, some of these studies may not be necessary, if fully justified.

Requirements for safety of traditional herbal medicines

Any assessment of traditional herbal medicines must be based on an unambiguous identification and characterization of the constituents. A literature search must be performed. This should include general literature such as traditional handbooks specific to the individual form of therapy, modern handbooks on phytotherapy, phytochemistry and pharmacognosy, articles published in scientific journals, official monographs such as WHO monographs, national monographs and other authoritative data related to herbal medicines, if available, database search in online or offline databases, e.g. WHO adverse drug reaction database, National Library of Medicine's Medline, etc. The search should not only focus on the specific herbal drug preparation, but should include different parts of the plant, related plant species and information originating from chemotaxonomy. Toxicological information on single ingredients should be assessed for its relevance to the herbal medicines.

Countries of the Eastern Mediterranean Region should share information on reliable sources of such information and submit proposals to the WHO Regional Office. In assessing these bibliographic data, particular attention should be given to the following aspects.

The characteristics and the type of preparation described in literature; does the literature refer to the same herbal preparation? Can the data be extrapolated, e.g. extract prepared with ethanol 40% vs. extract prepared with ethanol 60%? The extent of time and the extent of use of the herbal medicine; can the use have generated sufficient experience on safety? Is it plausible that risks would have been recognized empirically?

The need for additional data or additional new tests should be considered in the light of the information requirements for new substances. Many of the tests required for new substances may be replaced by documented experience. However, it should be carefully considered if all questions on toxicology raised for new substances could be answered sufficiently and in a plausible way by the available, general knowledge. A specific focus should be given to effects that cannot be readily detected empirically, e.g. genotoxicity.

The assessment should determine if there is sufficient information to guarantee safe use in vulnerable populations such as pregnant or lactating women and in small children. In assessing safety in pregnancy, information on traditional misuse, e.g. as an agent to induce abortion, should be assessed.

Minimum requirements for efficacy of herbal medicinal products

Efficacy claims for herbal medicinal products are made with respect to three areas.

- Acute disease: disease having a rapid onset and of relatively short duration.
- Chronic disease: disease having a slow onset and lasting for a long period of time.
- Health conditions.

In most cases, severe disease refers to a life-threatening disease, or one in which delayed treatment will lead to the deterioration of health or to loss of capacity to cure the disease, for example, in the case of severe cardiovascular diseases, gastrointestinal diseases, endocrine diseases, haematological diseases and immune disorders and diseases.

Problem-related health conditions sometimes recover without any medical intervention, e.g. loss of appetite, hay fever, menopause, etc. Efficacy of herbal medicinal products in this area could be

supported by data from well-established documentation including national pharmacopoeia and monographs, as well as other authoritative documents such as WHO monographs. Pre-clinical data of efficacy may not be necessary, but clinical data are required. If traditional use of products with well-established documentation reflects changes in medicinal indication, dosage form or mode of administration, the efficacy data and clinical data could be consulted (see Tables 1 and 2). The efficacy should be proven by pre-clinical data and clinical trials or well-established documentation. If the changes will impact the pharmacodynamics, pre-clinical study is needed.

Table 1. Summary of the efficacy data requirements for

Category of disease	Pre-clinical data of efficacy	Clinical data of efficacy	Other data or information required
Acute	Need	Control trial need	
Chronic	May need	Clinical date may be needed or may not be needed	
Health condition	May not be needed	May not be needed	Supported by well-established documents such as national pharmacopoeia and monographs

Table 2. Proposed requirements for efficacy data for evaluation of traditional herbal medicines with various changes

Traditional herbal medicines with well-established documentation			Pre-clinical data of efficacy[a]	Clinical data of efficacy[b]
No change, according to well-established documentation			No need	May not be needed
Changes	Dose		May be needed	Need
	Dosage form		May be needed	Need
	Mode of administration		May or may not be needed	Need
	Medicinal indication		Need	Need
	Herbal medicinal ingredients	Addition [c]	Need	Need
		Deletion [d]	May or may not be needed	May or may not be needed
		New combination [e]	Need	Need
	Medicinal plant part used		Need	Need
	Methods of preparation		Need	Need

[a] Pre-clinical data include efficacy of laboratory test and data on the standard dose and dosage form

[b] Clinical data of efficacy refer to clinical research in WHO General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine

[c] Addition: addition of one or more plants into traditionally used formula

[d] Deletion: deletion of one or more plants from traditionally used formula

[e] New combination: combination of two or more traditionally used formulas

Quality control of herbal medicinal products

Quality assurance is the shared responsibility of manufacturers and regulatory bodies. The manufacturers must adhere to good agricultural and collection practice (GACP), good manufacturing practices (GMP) and good laboratory practices (GLP) standards, establish appropriate specifications for their products, intermediates and starting materials and to compile well-structured comprehensive documentation on pharmaceutical development and testing. The producer should make a continuous effort to improve standards and to adapt them to the present state of knowledge. A cooperative approach between manufacturers, e.g. by establishing drug master-files for specifications and quality controls, is encouraged.

National health regulatory authorities have to establish guidance on all elements of quality assurance, evaluate dossiers and data submitted by the producers and to check post-marketing compliance of products with the specifications set out by the producer and GMP compliance. Regulatory authorities should facilitate access of good quality herbal medicines to the market by providing monographs in pharmacopoeias and by giving training and advice to small producers.

Implementation of such requirements is only possible if the production and marketing of herbal medicines is subject to an adequate registration scheme. Elements of quality assurance are adherence to good manufacturing, collecting, laboratory, practices guidelines, setting specifications and quality control.

Quality control for imported herbal medicinal products

All imported herbal medicinal products need to meet requirements of safety and efficacy and quality control regulation in importing countries. In order to control of the quality of imported herbal medicinal products, the following requirements should be taken into consideration:

- Licensing authority: licensing for importers, wholesalers, manufacturers and assemblers of imported herbal medicine products should be issued by national health regulatory authority.
- Licence type: the dealers of imported herbal medicinal products need to apply one or more of the licences depending on the type of business involved, such as licence of import, wholesalers, manufacturers and assemblers.
- Import licence: the onus of applying for an import licence shall rest with any local company who wish to import and sell imported herbal medicinal products in the importing countries.

The following information related to the importing company is required for application for an import licence:

- particulars of company
- particulars of person making application on behalf of company
- certificate of company/business registration
- store layout plan.

Importers are required to provide information on each imported herbal medicinal product handled by them and will be allowed to deal in approved products only. Detailed requirements for each imported herbal medicinal product comprise

- full product formula (in languages of the importing and exporting countries)
- a set of labels, pamphlet, carton and specimen sales pack
- particulars of manufacturer and assembler(s)
- manufacturer’s licence or certificate from health authority of manufacturing country/origin. An export certificate for the herbal medicinal product if the product is imported.

Based on the above-mentioned minimum requirements, each national health regulatory authority could develop its own requirements for quality control of imported herbal medicinal products.

Guidelines related to GACP and GMP

All parties involved in the production of herbal medicinal products should adhere to the principles set out in the WHO guidelines on good agriculture and collection practices (GACP) for medicinal plants and good manufacturing practices (GMP). Manufacturers of herbal medicines should be licensed and

registered. The quality assurance system should be adequate and proportionate to the type of production and the regional situation, e.g. agricultural production or industrial production. The implementation of a credible concept of quality assurance, e.g. identifying and eliminating potential sources of contamination, should be a primary goal rather than to implement all individual technical aspects.

In order to encourage implementation of GACP practices, incentives should be offered to producers of botanical raw material. Examples could be: giving technical and logistic support in the selection of appropriate sites for agricultural production, providing seeds and seedlings, selecting fertilizers and pesticides, providing or giving advice on machinery for harvesting and primary processing. The government should honour efforts by issuing certificates to those producers and materials that adhere to GACP standards based on the country situation.

It was suggested that the WHO guidelines for the manufacture of herbal medicinal products could be acceptable as a final draft for the Region. These guidelines will be handed over to the participants for study and comment. All participants are recommended to put in consideration the following areas while studying the WHO guidelines:

- raw materials control (refer to the GACP)
- starting material and intermediate substances
- in-process control: SOPs for processing methods should be mentioned
- finished product control: this should be performed with reference to raw material control, storing material control and intermediate substances control.

Guidelines related to quality control

The basis of quality control is the establishment of appropriate specifications and standards. Information on appropriate standards can be found in official pharmacopoeias, monographs, handbooks, etc**.**

In choosing analytical methods the availability and the robustness of the method must be considered. It may be preferable to use simple methods such as microscopic identification, thin layer chromatography; titration of active substance if a full validation of more sophisticated methods such as high performance liquid chromatography, gas chromatography and gas chromatography/mass spectrometry is not possible. If such advanced methods are used, a full validation for each test will be necessary.

Product information

The product information should include all necessary information on the proper use of the product. The following elements of information will usually be included:

- brand name of product
- quantitative list of active ingredients
- including plant names, part of plants used (i.e. Latin name)
- dosage form
- indications
- dosage: the minimum and maximum, as well as average dosage levels, must be stated (if appropriate, specified for children and pregnant women)
- mode of administration
- duration of use
- adverse effects, if any

- over-dosage information
- contraindications, warnings, precautions
- drug interactions if it is possible
- date of issue
- expiry date of product
- lot number
- name of manufacturer or company with full address.

Pharmacovigilance of herbal medicinal products

Adverse drug reaction report

Pharmacovigilance units are necessary to collect and assess information on herbal and traditional medicines. Where such units exist they should include and focus assessment of information on traditional and herbal medicines.

Each adverse drug reaction (ADR) report should be checked for a possible association with traditional or herbal medicines. Health professionals should be encouraged to ask their patients about the use of herbal and traditional medicines, including medicinal foods and to include information on concomitant use in their ADR.

Each herbal medicine must be clearly identified by its composition, brand name (if applicable) and dosage. If such information is missing in the ADR, the pharmacovigilance unit should immediately try to gather complete information, e.g. by asking the reporting health professional.

In analysing ADR reports, the following should be considered:

- A literature search on the herbal product, its constituents and any co-medication should be performed.

- The time–ADR relationship must be assessed:

  – When did the ADR occur?
  – Did the symptom occur when the herbal medication was started?
  – Has any co-medication beer used before the use of the herbal medicine without side effect?
  – Did the ADR occur when the co-medication was added to the herbal treatment?
  – Did the ADR stop when the herbal medicine was withdrawn?
  – Was the ADR reversible?
  – Did the ADR reappear after re-exposure?

- The dosage used should be compared with the traditional dosage described in literature:

  – Did the patient use a higher dose than recommended? Could it be intoxication rather than an ADR?
  – Is the dosage so low compared to the traditional dose that a link is not plausible? However be aware of allergic reaction
  – Were there any signs of allergic reactions, such as ashes, asthma, eosinophilia or angio-oedema?

- How common is the symptom with other diseases?

  – What is the prevalence of diseases with the same symptoms, e.g. hepatitis?
  – Can other causes be eliminated, such as virus markers or ethanol misuse in hepatitis?

- Search databases for similar case report for association with the same or similar herbal medicines or combination products. In case of suspicion, go to original reports because database file may not be complete and additional information may be found in the original report.
- If no association was found in literature, or if an association is not plausible because of the low dose, there could be a problem related to the product's quality. Check for possible adulteration, substitution, contamination, e.g. by mycotoxins, heavy metals, etc.

The assessment should be done in cooperation with a panel of comprising experts in pharmacognosy and toxicology and other health professionals, including traditional healers.

A clear conclusion on the causality should be made using the terms proposed by WHO guidelines related to drug safety monitoring.

Report system on how to set up or expand safety monitoring system for herbal medicinal products

- Promote education and awareness for the public and professionals.
- Establish a proper regulatory system for herbal medicine.
- Activate medicines information centres in health authorities to setup a special section and system for ADR of herbal medicines and any other possible medicine-related problems.
- Use existing tools (for conventional drugs) to collect and analyse data supported by a computerized system.
- Emphasize the scientific use of herbal medicines.
- Attempt to solve existing reporting system problems by using advanced database programmes.
- Request WHO assistance in ADR reporting system.
- Encourage the manufacturers and professionals, who produce and/or prescribe herbal medicines, to report ADR to the relevant authorities.

Control of advertisements of herbal medicinal products

The national authorities responsible for the regulation of herbal medicinal products and practices should authorize every advertisement before it reaches the public.

The regulatory authority should issue an advertising permit after satisfactory evaluation of the contents of the advert to ensure that the public gets the correct information about the product, devoid of ambiguous or false claims. The print and electronic media should be notified to ensure that every advertiser of herbal medicinal products obtains the advertising permit from the national authority before such advertisements are circulated.

Sharing the information on advertisement of herbal medicinal products and cooperation among the countries of the Region should be encouraged.