Pan American Health Organization
Regional Office of the World Health Organization

CONSULTATION FOR THE ESTABLISHMENT OF THE STEERING COMMITTEE FOR THE PAN AMERICAN CONFERENCES ON DRUG REGULATORY HARMONIZATION

REPORT

Caracas, Venezuela
14-15 January 1999

PAN AMERICAN HEALTH ORGANIZATION
WORLD HEALTH ORGANIZATION
PROGRAM ON ESSENTIAL DRUGS AND TECHNOLOGY

This meeting was organized by the Program on Essential Drugs and Technology and the United States Food and Drug Administration (FDA), which also provided funding for the meeting. Additional funding was received from the Latin American Federation of the Pharmaceutical Industry (FIFARMA).

DRUG REGULATION IN THE AMERICAS

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Report

I. OPENING SESSION

The meeting was opened by Dr. Enrique Fefer, Coordinator of the Program on Essential Drugs and Technology, (HSE) of PAHO/WHO. He began by outlining the agenda, pointing out the importance of giving continuity to regional activities relating to harmonization of drug regulations. He then briefly reviewed the background and activities that have been undertaken by the various economic integration groups in the Americas as well as the recommendations of the first Pan American Conference on Drug Regulatory Harmonization (Washington DC, November 1997). One of these recommendations was the convening of the meeting that is the subject of this report.

II. PRESENTATIONS

1. **Update on Regional Harmonization Activities.** Dr. J. Idanpaan-Heikkila (WHO) highlighted three main points in his presentation on this item: (1) WHO's responsibility in the harmonization activities in the various regions, including those being carried out in the Region of the Americas; (2) the importance of controlling the quality of raw materials used for pharmaceutical products. He cited as an example the recent case of ethylene glycol contamination in Haiti, emphasizing the responsibility of the supplier and the manufacturer to carry out quality controls to prevent this type of occurrence; and (3) the meetings of regulatory authorities sponsored by WHO (ICDRA), in which all regulatory authorities have participated, both from developed and developing countries. He indicated that the most recent of these meetings, held in Bahrein, had been attended by more than 100 participants, but that very few had been from Latin America, and he underscored the importance of encouraging greater active participation by regulatory authorities from this Region, especially as presenters.

2. **Presentations by Representatives of Countries and Pharmaceutical Associations**

Andean Community:

Venezuela. The Representative of Venezuela, Dr. Francisco Jimenez, outlined the progress made in the area of drug registration and control in the Andean Community,

indicating that in that Region: (a) the common drugs were identified, using the qualitative formula of the products as a basis; (b) the requirements for drug registration that must be approved in the participating countries were established; (c) the importance of the GMP standards in harmonization processes was affirmed; it was agreed to begin with the adoption of the GMP standards of WHO and a working group on the subject was formed; (d) the expedited registration requirements, applicable only to products made in the Andean Area, were approved; (e) the importance of strengthening the regulatory agencies was recognized; and (f) bioequivalence studies for pharmaceutical products are being considered. In Venezuela, guidelines for the implementation of bioequivalence studies have been developed and are pending for approval.

Colombia. The Representative of Colombia, Dr. Margarita Kirby, summed up the current situation with regard to the enforcement of current regulations. In regard to drug registration, in accordance with Decision 418 of the Andean Community, all products that pose a potential health risk, including drugs, must be registered. She explained that Resolution 3183 of 1995 adopted the GMPs and established regulations for the application of Decree 677/95, which in turn established the procedures for registration, quality control, and surveillance of drugs. The deadline for implementation of the GMPs was August 1998, although it was subsequently extended to February 2000. Currently, 22 pharmaceutical laboratories are certified in application of the GMPs. With regard to BE/BA studies, she indicated that the Review Commission, in its Proceedings 57/97, specified several dosage forms and groups of drugs for which these studies are required. Decree 219, issued 30 January 1998, regulated the quality control and surveillance procedures for cosmetic products. The GMPs for these products were adopted by means of Resolution 3112/98, and only administrative approval of the inspection guidelines remains pending.

MERCOSUR:

Argentina. The Representative of Argentina, Dr. Pablo Bazerque, stressed the importance of drug quality, efficacy, and safety and of ensuring safety and efficacy through the registration of products and quality through the registration of the companies. MERCOSUR does not have a common registration authority; rather, registration occurs at the national level. There is no automatic recognition of products from other MERCOSUR countries. There is no central agency, as in Europe. At present, there is only national registration and recognition of nationally registered products. The common drug list is being prepared, progress has been made in the registration of companies. GMPs based on those of WHO were approved, as were inspection guidelines, and joint training of inspectors is under way. Several joint inspections have been conducted (Argentina–Brazil and Argentina–Paraguay). The following elements are considered important in order to assure the quality of products: ongoing inspections of the quality of products on the market, post-marketing surveillance, control of biologicals (vaccines), equivalence of vaccines—especially those used in mass prevention programs—and control of biotechnology products. BE studies constitute another problem to be addressed. It is considered necessary to establish a timetable for implementation. There

are gray areas that require attention—such as the differentiation between food, drugs, and cosmetics—and it is of utmost importance to arrive at an agreement regarding these areas. He noted that this is also a problem in Europe. He emphasized that solutions should be developed at the subregional level, that there should be greater contact with the ICH, and that, given the repercussions of the ICH's decisions on the countries of the Region, Latin America should seek membership in this group, even if only as observers, in order to have the opportunity to make timely contributions.

Brazil. The Representative of Brazil, Dr. Silas Paulo Resende, reported that the Brazilian Congress had adopted a law creating the National Health Surveillance Agency (ANVS). Another law approved previously by the Congress defines what constitutes a reference drug or a similar or generic drug for the purpose of ensuring interchangeability among them. With the approval of the law creating the ANVS, a deadline was also established for updating drug registrations. Hence, the only MERCOSUR resolution that was pending has been incorporated into the national legislation. Efforts are under way to implement a policy on generics and certification of GMP with a view to ensuring the efficacy and quality of drugs. Training and certification of laboratory personnel to perform tests of bioavailability and bioequivalence are essential at this time. Assistance is being requested from countries that are more advanced in this area.

Central America:

Costa Rica. The Representative of Costa Rica, Dr. Marielos Morales, described several important subregional activities. One was a workshop on harmonization of health requirements (August 1998), which included requirements for drug registration, the pharmacopeia that will be adopted both for allopathic products and homeopathic products, and sampling and quality control tests. Labels were considered for liquid products, capsules, and others; requirements for third-party manufacturing of products and the labeling of these products; and the acceptance or non-acceptance of the package insert. Representatives of the pharmaceutical industry participated in the workshop. Another significant activity was an event carried out in September 1998 in Guatemala on specific cases of third-party manufacturing, in which each country made amendments to the original document, the final version of which is not yet available. The harmonization of criteria for drug registration in Central America, Panama and the Dominican Republic was another subject discussed at a sub-regional level. The third activity of importance is the workshop on harmonization of vaccine registration, a subject on which work is still under way. A fourth noteworthy activity is the harmonization of pharmacological standards for the registration of the common drugs in the sub-Region, which is in the final stages. In regard to Costa Rica, in particular, she noted that in August 1998 regulations were established that provide for recognition of drugs registered in Europe, Canada, Switzerland, and the United States, for which only marketing authorization is required.

Panama. The Representative of Panama, Dr. Jeeps Chillambo, reported that his country is in the process of prioritizing activities that can be decentralized and training personnel to carry out those activities. The Department of Pharmacy and Drugs is being reorganized

into specialized areas and has a large section (in the testing phase) devoted to drug control. The process of adapting legislation poses difficulties in terms of reconciling the interests of trade associations and political officials. The regulations governing pharmaceutical establishments are being reviewed and the computerized information network (SIAMED) is being established. He emphasized the need to assess each country's vulnerability with regard to situations and pointed out that adequate support often is not received from neighboring countries and other entities to facilitate a study. He also felt that the exchange of information should be more efficient and that the use of the Internet to submit complaints should be examined because the effort that is expended in investigating such complaints is not always justified.

North American Free Trade Agreement (NAFTA)

Mexico. The Representative of Mexico, Dr. Rafael Garcia Barrera, noted that Mexico had not been actively involved in harmonization processes and considered this meeting an opportunity to exchange information. There are currently difficulties in the classification of dietary and herbal supplements and skin and cosmetic products. In 1997, Mexico modified its General Health Law and in 1998 established an emergency guideline for the requirements for bioavailability, bioequivalence, and dissolution profile studies. The authorization of interchangeable generic drugs facilitates the registration of these products (made by a single laboratory that also makes the same product under a commercial trade name, which previously was not permitted) and establishes the possibility of third parties authorized to conduct bioequivalence studies. In labeling, generics must have the same characteristics as the brand-name drugs, with some differences, which are still being determined. Interchangeable products are included in the basic drug list (ME). The General Health Council is responsible for establishing procedures for testing the interchangeability of each dosage form and active principle in products. The catalogue will be available to physicians and pharmacies, where patients and the public will also have access to it.

United States. The Representative of the United States, Dr. Roger William indicated that his country is working closely with PAHO and is making progress on bilateral agreements with Canada and Mexico. The country already has bilateral agreements with Europe concerning recognition of inspections. This meeting afforded an opportunity to learn about the needs of, and collaborate with, other countries of the Americas.

Canada. Ms. Louise Déry, indicated that Canada has recently restructured its drug registration office. It has a Therapeutic Products Directorate and is interested in establishing relations with other regulatory authorities. The country would like to reach agreements on inspections and mutual recognition in the area of registration of medical devices.

Representatives of the Pharmaceutical Industry

Latin American Federation of the Pharmaceutical Industry (FIFARMA). The Representative of FIFARMA, Dr. Eduardo Tettamanzi, considered harmonization a challenge and pointed out that the countries have difficulties relating to technical problems, citing bioavailability as an example. He stressed that more thought should be given to how to adapt our legislation in accordance with the progress and quality improvement that is demanded, rather than focusing on what others should do to adapt their legislation to ours. He emphasized that what is important is continual progress and improvement.

Latin American Association of Pharmaceutical Industries (ALIFAR). The Representative of ALIFAR, Dr. Ruben Abete, was very impressed with Latin America's efforts to modernize. Considerable work remains to be done in the area of drug registration and manufacturing, and the interaction between countries is important in order to achieve safer and more efficacious drugs. In Latin America there is a reality: FTAA, MERCOSUR, Andean Community, and others. He felt that efforts to establish regional harmonization schemes should be extended to encompass the entire Region of the Americas. It is essential to look at what other countries are doing in order to make these experiences more advantageous for all.

3. European Drug Regulatory Harmonization. Mrs. Ariel North noted that in the European Union two processes or systems exist for the registration of new drugs: a centralized procedure for high-technology products (mainly new chemical entities) and biotechnology products and a procedure for mutual recognition (applied to generic drugs).

The centralized procedure is carried out through the European Agency for the Evaluation of Medicinal Products (EMEA) in London. This agency has evolved in three phases: first, the procedures were identified or defined (1995); then came a transitional phase in which the procedures began to be applied (1998); and finally, in a consolidation phase, the procedures will be reviewed and problems will be identified (2001). In the centralized procedure, the evaluation period is about 210 days. The Committee for Proprietary Medicinal Products (CPMP) resolves disputes on the basis of a vote of 20 out of the 30 Committee members. The decisions are applicable in all 15 countries of the European Union, including those that vote against them. One of the current concerns is informing on rejection decisions. The chairmanship of the CPMP rotates, changing every six months in accordance with the six-monthly rotation of the presidency of the Council of the European Union. The members are designated by the Member States as their representatives for purposes of contact, but experts may also be asked to serve on the Committee, when necessary. It holds regular meetings at the EMEA/London. The EMEA provides technical and logistic support (agenda, statistics, discussion sessions, etc.) but the Commission makes all final decisions.

Generic drugs are approved through a mutual recognition procedure. In this case, one of the greatest difficulties is that the dossiers may differ from country to country, which

creates problems in regard to interchangeability (substitution) because products may be labeled for different uses.

The authorizations granted by the EMEA remain in force for five years.

Guidelines for bioequivalence studies are under consideration and information is being exchanged on the studies that are carried out in the various member countries.

Drug registration is subject to the payment of a fee, 50% of which goes to support the EMEA and 50% to the two countries that carry out the evaluation. In 1997 the fees collected covered 49% of the EMEA's budget, in 1998 they covered 61.5%, and it is estimated that in 1999 the percentage will rise to 65.3%. The fee for registration in the centralized system for high-technology and biotechnology products is approximately $200,000. An additional fee is collected for the registration of each presentation and each dose.

4. The International Conference on Harmonization (ICH) and Regional Regulatory Harmonization Processes. Dr. Roger Williams reviewed the background of the ICH. The ICH Steering Committee is composed of 12 members, two each from the EU, Japan and the USA regulatory agencies, and representatives of their pharmaceutical industry. Observers (WHO, Switzerland, Canada) also participate. Its main areas of concern are quality, safety, efficacy, and regulatory communications. Very useful guidelines have been produced in each area. Those documents, through WHO, are consulted by experts and discussed in the ICDRA meetings. They are available on the Internet, and although they do not currently exist in Spanish, they could be translated.

The ICH experience has been successful. Subjects such as good manufacturing practices and good clinical practices are of great interest. The working groups are being expanded. China, India, and Canada are currently participating in the working group on quality. The participation of regional advisers from the offices of WHO is also being expanded, as is the distribution (for consultation) of draft documents.

III. FORMATION OF THE STEERING COMMITTEE

The group analyzed the importance of continuing and strengthening regulatory harmonization processes aimed at ensuring drug safety, efficacy, and quality in the Region of the Americas. The recommendation of the first Pan American Conference on the Drug Regulatory Harmonization was deemed to be of great importance for giving continuity to the process, and the formation of a Steering Committee (SC) was considered strategically necessary for this purpose.

It was also considered very important that the SC, once established, be officially recognized by the authorities of the countries in order to ensure the support and endorsement of the governments for the fulfillment of its responsibilities. The SC will have the following characteristics:

Mission

To coordinate, promote, facilitate, and monitor harmonization processes in the Americas with a view to assuring the quality, efficacy, and safety of drugs.

Objectives

- To maintain a constructive dialogue among regulatory agencies, the pharmaceutical industry, and other sectors involved, through periodic conferences.

- To promote and facilitate a common understanding of technical and scientific issues relating to drugs.

- To develop an information system and disseminate information on the progress of harmonization processes.

- To promote and facilitate technical and scientific cooperation among the countries.

- To determine the preparatory activities necessary for the Pan American Conferences on Harmonization and monitor implementation of the recommendations of those Conferences.

- To maintain ties with other entities concerned with regulatory harmonization.

Members

Representation:

The Committee will be made up of eleven (11) members: two representatives per geographic-economic integration bloc, who will be selected by the Pan American Conference on Drug Regulatory Harmonization. The membership of the Committee will include representatives of two countries from the MERCOSUR group, two from the North American Free Trade Agreement, two from Central America, and two from the Andean Area, one from CARICOM, as well as a representative of the Latin American Association of Pharmaceutical Industries (ALIFAR) and a representative of the Latin American Federation of the Pharmaceutical Industry (FIFARMA).

Secretariat:

The Pan American Health Organization will serve as the permanent secretariat for the Committee.

Observers:

The Committee will have the following observers:

a) Permanent observer: Member of the European Commission.
b) Countries not represented on the Committee may send an observer.
c) Both trade associations (ALIFAR and FIFARMA) may send an observer (in addition to their participating member).

The establishment of the SC must be approved by the Pan American Conference on Drug Regulatory Harmonization. The members of the SC will serve for the two years between one Pan American Conference on Drug Regulatory Harmonization and the next, and new members will be elected at each Conference. In the interim, the group participating in this advisory group meeting will serve as the ad hoc Steering Committee for the organization of the next Conference.

Members of the Steering Committee (ad hoc):

Representatives:

For the Andean Area:

Margarita Kirby, Assistant Director of Pharmaceutical Services and Laboratories, Bogotá, Colombia

Francisco Jiménez, Director of Health Surveillance. Ministry of Health and Social Welfare, Venezuela

For the Caribbean area (CARICOM):

To be designated

For the Central American area:

Marielos Morales, Department of Registration and Control. San José, Costa Rica.

Jeeps Chillambo, Department of Pharmacy and Drugs. Ministry of Health. Panama

For the North American Free Trade Agreement:

Louie Déry, Therapeutic Products Directorate,
Bureau of Policy and Coordination, Ottawa, Canada

Rafael García Barrera, Department of Drug Control, General Directorate for Control of Health Inputs, Ministry of Health, Mexico

Roger Williams, Deputy Center Director for Pharmaceutical Science, Center for Drug Evaluation and Research, Food and Drug Administration, United States of America

For MERCOSUR:

Dr. Pablo Bazerque
National Director of Drugs, Food, and Medical Technology (ANMAT)
Ministry of Health. Argentina

Silas Paulo Resende Gouveia, Director, Technical-Regulatory Department, Secretariat of Health Surveillance, Brazil

For the Trade Associations:

Rubén Abete, Latin American Association of Pharmaceutical Industries (ALIFAR)

Eduardo Tettamanzi. Latin American Federation of the Pharmaceutical Industry (FIFARMA)

Secretariat

Program on Essential Drugs, PAHO/WHO

Permanent Observer

Ariel North, European Community, Brussels, Belgium.

Operation

Frequency of meetings: The SC will meet no fewer than two (2) times between one Conference and the next (the term of office of its members), which are expected to be held every two years in the month of November.

Site of meetings: The site (city) of the SC meetings will be selected preferably on a rotating basis or by offer of the member countries. In any case, preference will be given to sites in which a conference, meeting, congress, conference or other international gathering is to be held immediately before or after the Conference and in which the members, in their professional capacity or as representatives of their agencies, are scheduled to participate.

Financing

Of the Steering Committee

It is considered important for the countries to assume financial commitments to support the Committee. It was decided that PAHO will send letters to the ministers in the member countries of the SC (the current participants), indicating that they have been named as members and requesting official confirmation. Should any country decline membership, another country from the same geographic integration group must be selected to replace it.

Of the Preparatory Activities and the Conferences

PAHO will contact ALIFAR and FIFARMA to request support for the second Conference and the preparatory activities. The countries and agencies are also invited to contribute, as the FDA did in financing the Caracas meeting.

IV. ORGANIZATION OF THE SECOND PAN AMERICAN CONFERENCE ON DRUG REGULATORY HARMONIZATION

Date:

The Conference will be held 3–4 November 1999 and will be a closed meeting (only invited participants may attend).

The Conference will be followed by a one-day symposium (5 November), which will be open to anyone who wishes to attend. The symposium will be organized by the AAPS and the FDA, with the participation of the Pan American Pharmacy Federation (FEPAFAR). PAHO and the FDA will contact both associations in order to organize the symposium.

Place:
Pan American Health Organization, Washington, D.C.
Site of the symposium: to be determined

Preliminary Agenda

DAY 1

1. Introductory Session

General Presentations:
- PAHO
- Steering Committee. Report
- Free Trade Area of the Americas
- WHO/ICDRA
- European Commission

2. Bioequivalence and generic products

Report of the Group of Experts

Preparatory Activity

Meeting of experts on bioequivalence, held in Caracas, January 1999.

3. Good Clinical Practices

- Presentation by WHO/ICH
- Presentation by ANMAT
- Panel: Argentina, Brazil, Mexico, United States
- Coordinator: Argentina.

Preparatory Activities:

a) ANMAT will prepare a document, which will be available on the Internet for consultation by all.
b) Working group on Good Clinical Practices, which will include representatives of the various geographic groups (MERCOSUR, Central America, Andean Community, and North American Free Trade Agreement). Objective: To prepare a document on GCP for the Americas.

DAY 2. Morning Session

1. Good Manufacturing Practices and Inspection

Presentation on FIFARMA study
Presentation of proposed guidelines for inspectors prepared by group of experts
Plenary discussion

Preparatory Activities:

a) FIFARMA will update the FIFARMA document presented at the first Conference and will include a component on the current status of GMP in the Americas
b) Group of experts, composed by representatives of the various geographic groups and coordinated by the FDA, will prepare a consensus document on the inspection guidelines
c) Contacts:
MERCOSUR: Martha Veloso
Andean Community: Ana Mercedes Guzmán/ Luisa Fernando Ponce de León
Central America: Sonia Cequeira

Reference materials:
FDA/WHO/ICH/Andean Countries /Central America/MERCOSUR

d) Development of a training program for GMP inspection in collaboration and with the participation of teaching institutions.
Note: The training program will be implemented after the Conference through a plan of action to be developed (if possible previously).

2. Counterfeit Drugs - Situation and Mechanisms to Combat Counterfeiting

Presentation of North American Free Trade Agreement (NAFTA) document. Canada. (The document is on the Internet in English and Spanish)
Presentation WHO.
Experiences: Argentina, Brazil, ALIFAR, FIFARMA
Panel: Discussion and plan of action
Coordinator: Brazil

DAY 2 . Afternoon Session

3. Classification of Products (Drugs)

Presentation by the FDA, Canada, and Mexico
Panel: Brazil, Costa Rica, Mexico, Venezuela, Representative of over-the-counter products of Mexico (AFAMELA).
Coordinator: Canada

The presentations will include experiences, classification criteria used, identification of problems, proposals for harmonizing criteria, and recommendations on the following products:

Prescription drugs
Over-the-counter drugs
Nutraceuticals and food
Cosmeceuticals
Herbal and phytotherapy products
Vitamins (drugs and dietary supplements)

5. Selection of the Steering Committee for the Pan American Conference on Drug Regulatory Harmonization

4. Conclusions and Recommendations to the Steering Committee