



PAN AMERICAN HEALTH ORGANIZATION  
WORLD HEALTH ORGANIZATION



## **34th SESSION OF THE SUBCOMMITTEE ON PLANNING AND PROGRAMMING OF THE EXECUTIVE COMMITTEE**

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### **PHARMACEUTICAL REGULATORY HARMONIZATION IN THE AMERICAS**

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Political and economic development in the Americas has resulted in a renewed interest in regional economic integration. The regulation of pharmaceuticals and the harmonization of technical standards have emerged as an important component of the economic integration discussion. The degree of progress in the area of harmonization of technical standards varies from one subregion to another and from one country to another.

Based on similar needs, other regions and at multiregional level a group of countries are working toward drug regulatory harmonization. In fact, the European Union developed a structure and system for harmonizing the laws and regulations of its member countries intended to promote both public health and the free circulation of pharmaceuticals within the European trade areas. Europe, Japan and the USA formed the International Conference on Harmonization (ICH) which is working toward drug regulatory harmonization.

In the Americas there is a need to promote harmonization and thus promote the health of the Region by facilitating the availability of safe, effective and quality pharmaceuticals. PAHO, with the collaboration of the pharmaceutical industry, held two conferences related to pharmaceutical regulatory harmonization in the Americas, to facilitate communication and exchange of information among all interested parties in drug regulation.

This issue is submitted to the Subcommittee on Planning and Programming to promote among its Members the implications and importance of the process on drug regulatory harmonization efforts in the Region of the Americas as a way to assure drug quality in a globalized pharmaceutical market; and to obtain the support of the Pan American Network for Drug Regulatory Harmonization and its Steering Committee.

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## **1. Introduction**

Pharmaceutical products (drugs and biologicals) intended to diagnose, prevent or treat diseases or conditions in humans are products whose availability is driven by research advances and national policies on research and regulation. The pharmaceutical industry seeks to be multinational and by necessity will need to comply with national requirements. Harmonization of technical requirements for development and registration of pharmaceuticals will reduce unnecessary and duplicative requirements. This should expedite the availability of pharmaceutical products and reduce the costs of their development. Thus, harmonization without compromising standards of safety and effectiveness is in the interest of the consumer and public health.

## **2. Current Situation**

### **2.1 *Global Harmonization: World Health Organization and the International Conference of Drug Regulatory Authorities***

The Constitution of the World Health Organization (1946) specifically directs WHO "...to develop, establish, and promote international standards with respect to food, biologics and pharmaceuticals and similar products." This has been accomplished through the work of Expert Technical Committees creating recommendations for internationally accepted standards, policies and reference materials. The International Conference of Drug Regulatory Authorities (ICDRA) conferences have been convened by WHO every two years since 1980 with the objectives of promoting harmonization, exchange of information and development of collaborative approaches to problems of common concern to all drug and biologic regulatory authorities in the world.

### **2.2 *European Harmonization***

The European Union, which to date includes full participation of 15 European countries, and observer status for others, developed a structure and system for harmonizing the laws and regulations of its member countries intended to promote both public health and the free circulation of pharmaceuticals within the European trade areas. European Council Regulation (EEC No. 2309/93 of 22 July 1993) established the European Agency for the Evaluation of Medicinal Products (EMA) to specifically oversee, coordinate and facilitate European harmonization of pharmaceutical requirements. The creation of the EMA was in large part due to the multinational focus of the pharmaceutical industry and the increasing cost and time for development of new medicines. Pharmaceutical companies needed to rely on an effective and efficient regulatory environment within the European Union to be fully competitive in developing products to promote public health.

### **2.3 *The International Conference of Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use***

In 1990 a unique project was initiated through the cooperative effort of the pharmaceutical regulators and research and development industry of three regions: the European Union, Japan, and the United States. The International Conference of Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) was established to improve through harmonization, the efficiency of the process for developing and registering new medicinal products in the three regions. This effort is aimed at ensuring that good quality, safe and effective pharmaceuticals are developed and registered in the most efficient and cost-effective manner. These activities, as stated in the ICH's 1990 Terms of Reference, "...are pursued in the interest of the consumer and public health to prevent unnecessary duplication of clinical trials in humans and to minimize the use of animal testing without compromising the regulatory obligations of safety and effectiveness". The ICH sponsors wanted to ensure transparency of its harmonization process and recognized the importance of the presence of observers from other regulatory authorities as a means of ensuring that the benefits of harmonization be utilized worldwide. To that end, WHO, Canada and the European Free Trade Area (EFTA) representatives were made permanent "observers" to the Steering Committee. Expert Working Groups of the ICH, including observers, were charged with the task of harmonizing the technical requirements identified as priorities by the ICH sponsors.

Recognizing the growing use and adoption of more than 40 guidelines developed in the first 10 years of ICH harmonization activities, in March 1999, the ICH Steering Committee created a subcommittee to focus specific attention on global cooperation. Of paramount importance, is the recognition by the ICH sponsors that close cooperation with WHO and support for WHO efforts is critical to ensure that the ICH achievements are readily available to all.

### **2.4 *Harmonization Activities in the Region of the Americas***

Political and economic development in the Americas has resulted in a renewed interest in regional economic integration. The regulation of pharmaceuticals and the harmonization of technical standards have emerged as an important component of the economic integration discussion. The degree of progress in the area of harmonization of technical standards varies from one subregion to another. There is a need to promote harmonization in the Americas and thus promote the health of the Region by facilitating the availability of safe, effective and quality pharmaceuticals. In addition, both the national authorities and the pharmaceutical industry recognize that in order to participate

in the world market, the Region, as a prerequisite, must meet international standards on the quality of pharmaceuticals, as well as have effective registration (licensing) processes.

#### 2.4.1 *The North American Free Trade Agreement*

To date in the North American Free Trade Agreement (NAFTA), established in 1994, the topic of the regulation of pharmaceuticals has focussed on information exchange such as regulatory matters, Good Clinical Practices (GCPs), postmarketing surveillance and adverse event reports, approval of new products, and joint reviews. These discussions are supportive efforts in the development of harmonization within the current regulatory requirements in each of the three NAFTA countries (Canada, Mexico and the USA).

#### 2.4.2 *MERCOSUR*

The Mercado Común del Sur (MERCOSUR), established in 1991 by Argentina, Brazil, Uruguay and Paraguay, reflects the most structured effort among the trade groups for regulatory harmonization of pharmaceuticals. The technical work is carried out through working subgroups, one of which focuses on technical standards. PAHO is an official observer to the meetings of this subgroup. There has been important progress such as the establishment of work mechanics at the technical level, the definition of priority subjects, and the acceptance of some common standards, some of which are based on recommendations of WHO such as Good Manufacturer Practices (GMPs). Difficulties lie in the adoption and implementation of MERCOSUR agreements and resolutions by participant countries.

#### 2.4.3 *The Andean Group*

The Andean Group, established in 1969 and which includes Bolivia, Colombia, Ecuador, Peru and Venezuela, has been attempting with limited success since the 1970s to develop a common market, despite several agreed upon proposals. Drug policy, drug regulation and common registration have been topics openly and widely discussed by national drug regulators. Organizations such as the Convenio Hipólito Unanue and the Secretariat of the Andean Community (formerly Cartagena Agreement), promoted and sponsored a meeting seeking pharmaceutical regulatory harmonization, and PAHO provided technical support for several activities in this subregion. Of particular interest are the bilateral agreements between countries such as one between Colombia and Venezuela on GMPs.

#### 2.4.4 *The Caribbean Community*

In the Caribbean Community (CARICOM) established in 1973, a legal or administrative framework for pharmaceutical regulatory harmonization has yet to be established. However, the Caribbean Regional Drug Testing Laboratory is responsible for drug quality analysis in the subregion and its Technical Committee meets twice a year. Last year (1999), CARICOM hosted a meeting on regulatory issues sponsored by PAHO.

#### 2.4.5 *Central America Integration System*

Economic integration in the Central America area is being sought by the Central America Integration System (SICA), established in 1961 with Costa Rica, El Salvador, Guatemala, Honduras and Nicaragua as members. There have been several attempts to establish a free trade in pharmaceuticals, but without success. Drug regulatory harmonization in this subregion began in 1985 as part of several projects on essential drugs. In 1993, the need for harmonization and the protection of consumer health were recognized in the Protocol of Economic Integration, signed by the presidents of Central America. However, since there is no subregional legal or administrative framework for participating countries to adopt the decisions of subregional technical meetings, the implementation of those agreements depends on the interest and political capacity of the regulatory authorities. Pharmaceutical regulatory harmonization processes are, for the most part, supported by PAHO and during recent years, some activities are further being supported by the pharmaceutical industry. Harmonization efforts have focussed on pharmaceutical registration, GMP inspections and quality control.

### **3. PAHO Activities Related to Drug Regulatory Harmonization in the Americas**

PAHO convened a series of three conferences related to pharmaceutical regulatory harmonization in the Americas. These conferences, which included large numbers of regulators, and representatives from the industry, consumer groups, regional professional associations, and other interested groups, from all regions of the Americas, facilitated communication and exchange of information.

As a result of these conferences, harmonization activities were recognized as important areas to be focused on to ensure that national authorities in the Region have access to state of the art information. The summary of these meetings and their outcomes follow:

### **3.1 *Pan American Conference on Drug Regulatory Harmonization***

*Washington, D.C., 17-20 November 1997*

Conference participants acknowledged the necessity of continuing harmonization processes under way through the specific agencies and mechanisms currently operating in the Region, such as CARICOM, LAIA, MERCOSUR, NAFTA, and the Andean Community.

It was unanimously recommended that a hemispheric forum be established, with PAHO as its Secretariat, to facilitate communication among the different subregional blocs on the subject of drug regulation. The importance of having a Steering Committee in which the subregional groups that are active in the regulatory harmonization process are represented was emphasized. The forum should include all stakeholders involved in addressing the problems connected with pharmaceuticals: the regulatory authorities, industry (domestic and multinational), representatives of the integration entities, consumers, and professional associations.

Further recommendations suggested that terms of reference for the forum and the Steering Committee could be developed by mutual agreement and could cover the following areas: 1) structure and operations; 2) legal/administrative/policy regulatory topics; 3) information exchange and communications, focusing on Internet access and translations; 4) training to build expertise; and 5) other general topics of mutual interest.

### **3.2 *Center for Drug Evaluation and Research, FDA: Meeting of Americas' Regulators***

*Washington, D.C., 21 November 1997*

Taking advantage of the Pan American Conference on Drug Regulatory Harmonization, in November 1997, the FDA's Center for Drug Evaluation and Research, with PAHO's assistance, arranged a meeting of Americas' Regulators.

The intent of the meeting was to discuss further harmonization strategies for selected science/technical topics in the Americas (continuation of discussion from PAHO meeting) and to consider 'doable' short-term activities on selected science/technical topics that could support long-term regulatory harmonization efforts in the Americas.

Attendees determined a series of science, technical and general strategy topics worthy of cooperative efforts. The topics included bioavailability and bioequivalence (BA/BE), GMP's, control laboratories/surveillance, and enhanced communication between the Regulators and countries of the Americas.

**3.3 *Consultation for the Establishment of the Steering Committee for the Pan American Conferences on Drug Regulatory Harmonization***  
*Caracas, Venezuela, 14-15 January 1999*

Participants analyzed the importance of continuing and strengthening regulatory harmonization processes aimed at ensuring the quality, efficacy, and safety of drugs in 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 was considered strategically necessary for this purpose. It was also considered very important that the Steering Committee, 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.

**3.4 *The Second Pan American Conference on Drug Regulatory Harmonization***  
*Washington, D.C., 2-5 November 1999*

The Second Pan American Conference on Drug Regulatory Harmonization recognized that progress had been made since the first Conference on drug regulatory harmonization in the Region, although it also suggested that a greater, more continuous effort should be made. Pharmaceutical topics discussed at the conference included: bioequivalence, good clinical practices, good manufacturing practices, counterfeit products, and categorization of drug classes. Further work on these topics was recommended with harmonization efforts considered, where feasible.

The Conference participants concluded that (in part):

- Harmonization should be understood as the search for common ground within the framework of recognized standards, taking into account the existence of different political, health, and legislative realities among the countries of the Region.
- The mission of the Conferences is to promote regulatory harmonization for all aspects of quality, safety and efficacy of pharmaceutical products as a contribution to the quality of life and health care of the citizens of the countries of the Americas.
- A “Pan American Network for Drug Regulatory Harmonization” with biennial Pan American conferences should be established to provide an open forum for interested parties.

- A steering committee should be formed to enable progress between Conferences by coordinating, promoting, facilitating and monitoring harmonization processes in the Americas.

### **3.5 *First Meeting of Pan American Network for Drug Regulatory Harmonization Steering Committee***

*Proposed for April, 2000*

The main objective of this meeting will be to develop a two-year work plan according to the recommendations of the Second Pan-American Conference on Regulatory Harmonization.

#### **4. Recommendations for Proposed Actions: How PAHO and the Countries of the Americas Should Proceed to Achieve Better Harmonization of Pharmaceutical Regulation**

- Every effort should be extended by PAHO, and the countries to endorse and assure the success of the Pan American Network for Drug Regulatory Harmonization and the biennial Pan American Conferences in their efforts towards pharmaceutical harmonization. Providing an open forum for interested parties (e.g., regulators, industry, consumer representatives), to discuss the progress of harmonization will ensure the successful adoption and implementation of harmonized outcomes.
- It is of utmost importance that the highest appropriate level authorities of the countries officially endorse the Steering Committee in order to ensure the support and endorsement of the work of the Steering Committee and working groups.
- PAHO should provide administrative support for the Network, the Conference and the Steering Committee. Resources should be allocated to enable this activity.
- PAHO should increase support to the countries of the Region by strengthening the capacity of the regulatory authorities involved in the harmonization process to participate, adopt and implement the recommendations. For those countries with less developed regulatory infrastructures, PAHO should promote the adoption of procedures that facilitate regulation, e.g., The WHO Certification Scheme for Pharmaceutical Products Moving in International Commerce.
- The health authorities of the Americas should make a commitment to move forward with the implementation of scientific standards, at the normative level,

approximating international recommendations. Work schedules should be established to expedite the regional goals for harmonization with initiatives for cooperation in pharmaceutical regulatory harmonization in the subregional blocs supported within the framework of the economic integration processes. The participation of academia and the private sector should be promoted to provide the infrastructure with the necessary human resources (Annex A).

#### **5. Action Requested of the Subcommittee on Planning and Programming**

This proposal for continuing and enhancing pharmaceutical regulatory harmonization efforts in the Americas is submitted for the consideration of the Subcommittee on Planning and Programming. To promote the importance of harmonization efforts in the Region of the Americas it is imperative to enlist the political will of the national authorities in support of the Pan American Network for Drug Regulatory Harmonization and its Steering Committee. To assure the success of these entities, the Subcommittee should recommend that various means of financial support be explored.

#### **6. Budget and other Issues**

Financing to support the Steering Committee and the Pan American Network is necessary if harmonization efforts are to progress. Financing could come from government, industry, registration fees from conferences (the ICH model), and other sources. PAHO and WHO might be able to provide resources, but given general resource constraints these should always be considered supplementary, supplied through extra budgetary sources (Annex B).

Annexes

**Pan American Network for Drug Regulatory Harmonization  
Working Groups, 2000-2001**

<b>Topics</b>	<b>Members</b>	<b>Scope</b>	<b>Outcomes/Indicators</b>	<b>Timeframe</b>
BA/BE	<ul style="list-style-type: none"> <li>• Regulators</li> <li>• Industry</li> <li>• Academia</li> </ul>	<ul style="list-style-type: none"> <li>• Three meetings at subregional level based on the Caracas report</li> <li>• Consolidation of conclusions and recommendations from the meetings identifying common ground and differences</li> </ul>	<ul style="list-style-type: none"> <li>• Report</li> <li>• Number of trained professionals</li> <li>• Regulatory agencies with regulations</li> <li>• Number of studies being developed</li> </ul>	<ul style="list-style-type: none"> <li>• Next conference: Nov. 2001</li> </ul>
CLASSIFICATION	<ul style="list-style-type: none"> <li>• Regulators</li> </ul>	<ul style="list-style-type: none"> <li>• Comparison study on classification criteria of all countries</li> <li>• Survey on key issues</li> <li>• Recommendations.</li> </ul>	<ul style="list-style-type: none"> <li>• Report</li> <li>• Countries with reviewed criteria</li> </ul>	<ul style="list-style-type: none"> <li>• Next conference: Nov 2001</li> </ul>
COUNTERFEIT	<ul style="list-style-type: none"> <li>• Regulators</li> <li>• Industry</li> <li>• Consumer group</li> </ul>	<ul style="list-style-type: none"> <li>• Partnership mechanism between countries and international organizations to help combat the problem</li> </ul>	<ul style="list-style-type: none"> <li>• Work plan</li> </ul>	<ul style="list-style-type: none"> <li>• Next conference: Nov 2001</li> </ul>
GOOD CLINICAL PRACTICES (GCP)	<ul style="list-style-type: none"> <li>• Industry</li> <li>• Regulators</li> <li>• Academia</li> </ul>	<ul style="list-style-type: none"> <li>• Situation analysis on GCP in the Americas</li> <li>• Mechanism to follow up on the implementation of GCP (Buenos Aires)</li> <li>• Identify training program for regulators</li> </ul>	<ul style="list-style-type: none"> <li>• Report</li> <li>• Work plan</li> <li>• Report</li> <li>• Recommendations and Program</li> <li>• Number of trained professionals</li> </ul>	<ul style="list-style-type: none"> <li>• Next conference: Nov 2001</li> </ul>
GOOD MANUFACTURING PRACTICES (GMP)	<ul style="list-style-type: none"> <li>• Academia</li> <li>• Industry</li> <li>• Regulators</li> </ul>	<ul style="list-style-type: none"> <li>• Training program design</li> <li>• Implementation of the Training Program</li> <li>• Mechanism for Monitoring system for GMP implementation</li> <li>• Validation course (Canada)</li> </ul>	<ul style="list-style-type: none"> <li>• Implementation of the TP in at least five countries</li> <li>• Proposal/work plan</li> <li>• Number of trained professionals</li> </ul>	<ul style="list-style-type: none"> <li>• Next conference: Nov 2001</li> </ul>
GOOD PHARMACY PRACTICES	<ul style="list-style-type: none"> <li>• Regulators</li> <li>• Professional Associations</li> <li>• Academia</li> </ul>	<ul style="list-style-type: none"> <li>• No Working Group needed</li> </ul>	<ul style="list-style-type: none"> <li>• Presentation from Pharmaceutical Forum of the Americas at the Third Conference</li> </ul>	<ul style="list-style-type: none"> <li>• Next conference: Nov 2001</li> </ul>
PHARMACOPOEIA	<ul style="list-style-type: none"> <li>• Pharmacopoeia members</li> <li>• Regulators</li> <li>• Industry</li> </ul>	<ul style="list-style-type: none"> <li>• Mechanism for communication network</li> </ul>	<ul style="list-style-type: none"> <li>• Work plan</li> <li>• Network established</li> </ul>	<ul style="list-style-type: none"> <li>• Next conference: Nov 2001</li> </ul>
REGIONAL ENTITY	<ul style="list-style-type: none"> <li>• Regulators</li> </ul>	<ul style="list-style-type: none"> <li>• Develop a work plan for a feasibility study</li> </ul>	<ul style="list-style-type: none"> <li>• Work plan proposal</li> </ul>	<ul style="list-style-type: none"> <li>• Next conference: 2001</li> </ul>

**ESTIMATED BIENNIAL BUDGET FOR THE PROPOSED  
WORK PLAN 2000-2001 FOR DRUG REGULATORY HARMONIZATION**

<b>ACTIVITIES</b>	<b>NUMBER OF MEETINGS</b>	<b>ESTIMATED BUDGET US\$</b>
CONFERENCE	ONE	100,000
STEERING COMMITTEE	THREE	40,000
WORKING GROUPS	EIGHT	160,000
<b>TOTAL</b>		<b>300,000</b>