WORKING GROUP ON DRUG REGISTRATION

Background[1]

The main objective of the Pharmaceutical Policy of the vast majority of the countries of the Americas is to guarantee the access to essential quality, effective and safety drugs, and that these drugs are used rationally. Since drugs are a public good with a high social value, indispensable in the provision of health care, and because patients and health professionals that prescribe and/or dispense them are not able to assess drug quality, efficacy and safety, it is the State responsibility, through their national regulatory systems or their regulatory authorities to assure all drugs met approved criteria for quality, efficacy and safety[2].

Internationally it is accepted that drug production and distribution require public authorization and oversight. These activities are divided into three components: a) product registration, including authorization for the marketing of drugs and monitoring of their efficacy and safety post marketing; b) regulation of drug production, importation, and distribution; and c) regulation of drug marketing and drug information.[3],[4]

The majority of the countries of the Americas have developed during the past several years legislations with regard to the drug registration, inspection, drug control, and monitoring. In regard to drug registration, the regulatory system varies from country to country with regard to: drug classification (medicinal plants, biologicals, homeopathic, etc.); the requirements requested for their evaluation and registration (pharmaceutical documentation, bio-pharmaceutics, preclinical and clinical data, etc.). They also vary according to the degree of new development (new chemical entities, generic, etc.) and with regard to the rigorousness with which is addressed the analysis of the available and/or requested documentation. There are countries in which the approval of drugs is conditioned to which it is approved or not in a list of countries, known as of reference, or of high regulatory development and, in some of them it is enough to get only a Free sale certificate, or a Certificate of Pharmaceutical Product in accordance with the World Health Organization (WHO) model or the Certificate of Approval of the country of reference to authorize its marketing; while in other countries it is requested suffices and completes documentation in order to evaluate them for drug approval.

On other hand, the differences in the requirements requested for the labeling and insert are reason for controversy, and constitute tangible difficulties, from both health and commercial standpoint. Another aspect in which there are major variations in the Region it is in the times used for the drug approval and registration, which range among the 7 days in some until 2 years in others.

These differences of criteria in the aforementioned aspects has generated over the last years a series of initiatives on the part of international Agencies, both of the health sector and

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[1] *Prepared by the Secretariat for the IV Pan American Conference on Drug Regulatory Harmonization. March 2005*
[2] *Regulatory Support Series. No 6 WHO 2001*
[3] *WHO Medicines Strategy 2004-2007: Coutries at the Core.*
[4] WHO. *The World Medicines Situation*, 2004.

of the economics sector to find mechanisms that on the one hand ensure the availability of drugs at the national and international levels with the necessary health standards for guaranteeing the Public Health and on the other hand that these requirements are sufficiently similar so that it facilitates the international trade of the drugs in the shorter possible time. These concerns have generated at the world level a series of initiatives within which are counted:

In 1996 the Ministers of Health adopted a resolution calling on the Director-General of the WHO to continue the work of that organization toward the development and harmonization of standards to strengthen drug regulation mechanisms.[5]

WHO has contributed to the global harmonization of essential pharmaceutical regulation instruments including: the International Common Denominations proposed by the WHO; the International Pharmacopeia; standards of Good Manufacturing Practices (GMPs); the certification system for quality control of pharmaceutical products traded internationally; Good Clinical Practice (GCP) standards, and guidelines on requirements for the registration of interchangeable generic drugs.[6]. It also includes the automated system for drug registration, the guideline for the Evaluation of Medicinal Products used in the Self-medication, among others[7].

For the dissemination and knowledge of this normative WHO organizes every other year WHO organizes the International Conference of Drug Regulatory Authorities (ICDRA), at which drug regulatory authorities of developed and developing WHO member countries meet to discuss topics of common interest on pharmaceutical regulation.

In 1990 the International Conference for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was established. This forum brings together the health authorities and pharmaceutical industries of the United States, Japan, and the European Union. At the Conference, topics associated with drug quality, safety, and new drug efficacy are debated. Today the ICH has a Global Cooperation Group (GCG), which includes representatives of a number of different harmonization initiatives in various regions, the WHO, and selected countries. The purpose of the GCG is to promote advances aimed at achieving harmonization initiatives in different parts of the world.

Significant regional initiatives to harmonize drug registration include the Association of South East Asian Nations (ASEAN) and the Collaboration Agreement of Drug Regulatory Authorities in European Union Associated Countries (CADREAC). With regard to harmonization processes in other regions, the European Union, which began functioning in 1995, specifically address the topic of drug registration and has met with concrete results. Today it has a centralized system in place for registering drugs in the regional market, whereas EU countries continue to operate their own systems for products whose circulation is limited to national markets.[8]

In the America there are several initiatives of harmonization of requirements for drug registration, promoted basically by the groups of economic integration which have been in charge of accelerating them. In fact, in the Region of the Americas drug registration is a topic

[5] *OPS. El Proceso deArmonización de la Reglamentación Farmacéutica en las Américas, 1997.*
[6] *Ibid.*
[7] *Ibid*
[8] *For information on EMEA log onto to: www.emea.org*

that is being addressed by economic integration groups, which, to date, have reached various degrees of development, although there has been no specific agreement on requirements for the registration of pharmaceutical products. Those groups are:

a) The North American Free Trade Agreement (NAFTA), currently is still limited to the exchange of information as an instrument for promoting harmonization, while respecting the regulation requirements in effect in each of its members (Canada, Mexico, and the United States);

b) The Southern Cone Common Market (MERCOSUR) is made up of Argentina, Brazil, Paraguay, and Uruguay. Chile and Bolivia participate in MERCOSUR technical discussions as observers, but not members. This is the most structured integration process to date in the Americas, having set up the political, administrative, and technical mechanisms necessary for complying with the mandate of establishing a common market. It has institutions in place to support the integration process and joint negotiations with third countries or economic blocs. The working group on technical regulation has addressed issues on food and drugs. MERCOSUR does not have specific agreements to harmonize drug registration requirements;

c) The Central American Integration System (CAIS) made up of Costa Rica, El Salvador, Honduras, Guatemala, and Nicaragua, through their Customs Union, have formed a working group on drugs that has harmonized aspects such as drug registration requirements, stability, labeling, and an alphanumeric code for authorized drugs. Recently they approved mutual recognition of drug registration among Guatemala, El Salvador, and Honduras, for pharmaceutical products made in these countries;

d) The Andean Community of Nations (CAN). Although this system begin operating in 1997 with a view to establishing a Common Market by 2005 for the free circulation of goods, services, capital, and people, its true beginnings date back to the early 1990s through the Cartagena Agreement and the Hipólito Unanue Agreement (Andean agency of cooperation in health). The CAN is a sub-regional organization with international legal status made up of Bolivia, Colombia, Ecuador, Peru and Venezuela and made up of the bodies and institutions of the `Andean Integration System` (AIS). In regard to the harmonization of requirements of drug registration it has not been significant progress, except for what has been harmonized in the framework of the Hipólito Unanue, which in 1994 harmonized the System of Andean Registration of Medication, which never was approved nor was implemented[9];

e) The Caribbean Community (CARICOM) has no legal or administrative framework for drug harmonization. However, there is a Technical Advisory Committee of the Caribbean Regional Laboratory for Drug Analysis, which is responsible for monitoring drug quality in the subregion. The Technical Advisory Committee meets biannually.

From the regional standpoint, at the First Pan American Conference on Drug Regulatory Harmonization, the participants reiterated the need for prioritizing sanitary considerations within trade and economic integration processes. Moreover the Conference recognized the need to develop standardized criteria for evaluating and authorizing the marketing of drugs, as well as the need to strengthen the operational capacity and efficiency of drug regulatory authorities, recommending to this end the establishment of a hemispheric forum to coordinate

[9] *CAM: Comité Asesor de Medicamentos del Convenio Hipólito Unanue. Informe de reunión. Caracas, Venezuela 1994.*

the different subregional blocs on issues of drug regulation, and that PAHO act as the secretariat for this forum.[10]

At the Second Pan American Conference on Drug Regulatory Harmonization approval was given to the formation of the Pan American Network on Drug Regulatory Harmonization (PARF Network), the holding of biannual Pan American Conferences as an open forum of the different interested parties, and the formation of a Steering Committee to follow up on the recommendations of these conferences.[11] At this Conference, the recommendation was made to prepare a feasibility study on a system or regional mechanism for drug registration that, once analyzed by the subregional systems of integration would be recognized by the countries of the Region.[12] Implementation of that study was postponed by the Executive Committee, which considered that the proposal should not go forward until progress had been made toward the harmonization of sanitary registration requirements[13].

At that time, it was recommended that PAHO/WHO continue and increase support to the countries, especially those with the least amount of progress in developing the process of harmonization, and to strengthen their regulatory authorities. This was done to encourage regulatory authorities to become actively involved in the commitment to implement scientific standards, make progress on national recommendations, establish a timetable of work for regional harmonization goals, and to stimulate the involvement of academia and the private sector in providing the necessary human and infrastructure resources.

At the Third Pan American Conference it was recommended that the PARF Network continue supporting the working groups that began operations, and to initiate the work of those groups that had been identified as important and urgent according to the selection process carried out in the Conference, which included the formation of the Drug Registration Working Group.[14]

Pursuant to the recommendations of the III Conference, it was established a Working Group in Drug Registration, which prepared a survey on technical and legal requirements for drug registration that the different countries could be requesting and evaluating for the granting registration of drugs. During August 2003 to August 2004, the group was devoted to implementing the survey, identifying the requirements that the countries of the Region request in their drug registration process, determining the possible gaps existing in this matter. Once concluded that study, the GT/Drug Registration analyzed the data and formulated a proposal of harmonized requirements for drug registration. This proposal has among its objectives to recommend to the countries the necessary and sufficient requirements so that the Drug Registration Process becomes a guarantee to the Public Health, ensuring in each case, in accordance with the degree of innovation (new chemical entities, generic drug, new formulation, new form of dosage etc.) and to the type of drug (pharmaceutical Product, Biological), the safety, efficacy, and drug quality marketed in the regional market. Moreover, such proposal tries to homogenize the labeling requirements in the Region, which will favor the availability of drugs in more immediate form, facilitating the market expanded between countries.

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[10] *First Pan American Conference on Drug Regulatory Harmonization, 1997.*
[11] *Second Pan American Conference on Drug Regulatory Harmonization, 1999.*
[12] *Ibid*
[13] *Meeting of the Executive Committee of the Pan American Network for Drug Regulatory Harmonization. San Juan de Puerto Rico, 2000.*
[14] *Third Pan American Conference on Drug Regulatory Harmonization. 2002.*

The proposal encompasses the drug registration requirements for new or generic drugs. In this regard, it bears mentioning that registration requirements for similar or generic products were made uniform. Accordingly, there is no distinction between the two products (similar and generics) since, from the sanitary standpoint, there should be no differences in requirements for drug quality. The proposal also covers the registration of new drug dosages, new concentrations, new combinations, and registry renewal. It also includes a proposal of requirements for the registration of biologicals (vaccines).