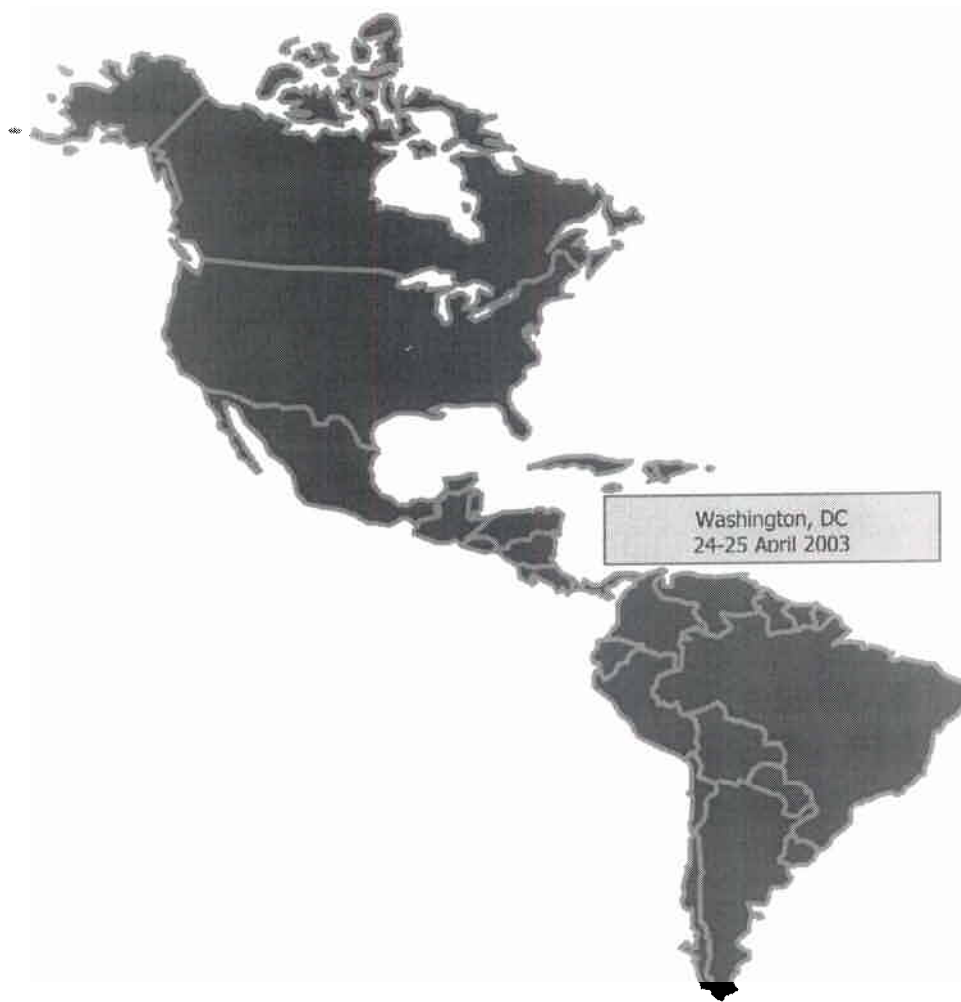


EVALUATION OF MULTI-SOURCE PHARMACEUTICAL PRODUCTS: SPECIAL FOCUS ON ANTIRETROVIRAL DRUGS



*Pan American Health Organization
Regional Office of the
World Health Organization*



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WHO/PAHO**

**Washington, D.C.
24-25 April 2002**

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INTRODUCTION

A workshop on the Evaluation of Multi-Source Pharmaceutical Products with Special Focus on Antiretroviral Drugs (ARVs) was convened as a pre-conference activity of the III Pan American Conference on Drug Regulation Harmonization.

The workshop was organized jointly with the WHO Quality and Safety Program of the Medicine Department and the Regional Program on Essential Drugs in the Region of the Americas. The main objectives of the workshop were to:

1. Analyze the basic quality principles of multi-source pharmaceutical products;
2. Present the results of a WHO pre-qualification project to increase access to antiretroviral drugs; and
3. Analyze and formulate recommendations, taking into consideration the particular conditions in each country of the Region.

Workshop participants included experts that had participated in the pre-qualification project, conducted by QSM/EDM/WHO and the national drug regulatory authorities of various countries of the Region of the Americas.

During the presentation, participants discussed the relevance and implications of the project's results and formulated several recommendations for the drug regulatory authorities and for WHO/HQ, as well as for PAHO/WHO to consider in their cooperation programs and projects.

PARTICIPANTS

SPEAKERS

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- **Maryam Mehmandoust**, Doctor of Organic Chemistry, Pharmaceutical Evaluation Expert, Evaluation of Pharmaceutical Drug Quality, Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS - French Agency for Health Care Product Control Standards), France
- **Conrad Pereira**, Health Canada, Canada
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CONCLUSIONS AND RECOMMENDATIONS

1. All pharmaceuticals in the market, whether from multiple sources (generic) or another type of product—including innovative products and those known in many countries as “similar” products, should be subjected to the same quality requirements.
2. Successful implementation of generic drug policy in many cases may imply capacity building in the areas of regulation, technology, infrastructure, and human resources development.
3. The quality of generic drugs is fundamental. It has been confirmed that when such products do not meet quality standards, they can undermine user confidence. Thus, it is necessary to draft policies that promote the use of generic drugs, while ensuring that they meet quality criteria.
4. In some cases, there are differences between the innovative product (used as a reference standard) manufactured in the country of origin and the drug produced and marketed locally. Effort should be made to prevent this situation.
5. Regulatory authorities should develop a strategy to address adequately the lack of control over Active Pharmaceutical Ingredients (API). In this regard, WHO technical support should be strengthened through the establishment of programs to control Active Pharmaceutical Ingredients (API). The first action should be the dissemination of the WHO guidelines for the control of API of different origins. Efforts must be directed to raising awareness of the problem and promoting the search for solutions.
6. In regard to antiretrovirals, strategies are needed to regulate active pharmaceutical ingredients (API), bearing in mind that only three antiretrovirals are included in internationally recognized pharmacopoeias. A first step could be the development of guidelines to control through documentation, followed by communication with regulatory agencies in the exporting countries.
7. The certification of foreign manufacturers should be analyzed, as well as the decisions made to promote mutual recognition, inspections, and verification by the authorities of the importing country.
8. While it is recognized that in the case of antiretrovirals the emphasis is on bioequivalence (BE) because other methods cannot be used, there are various methods for demonstrating bioequivalence, *i.e.*, in vitro analysis (dissolution test). It was recognized the importance of BE studies in antiretrovirals since those products constitute a critical drug group to the resistance problems that are already emerging. In the future and for other drugs, other methods can be applied.
9. Efforts should be made to promote standardization of the qualified centers offering bioequivalence (BE) services. In this regard, PAHO/WHO and WHO/HQ could provide support.
10. The value of having a list of WHO pre-qualified products that will be permanently updated and accessible on its web page was recognized; and drug regulatory agencies should be encouraged to participate in the WHO pre-qualification process.

11. Technical cooperation among countries should be strengthened to draw on the practical knowledge that some regulatory agencies, e.g., the U.S. FDA have amassed in different fields such as GMP and BE studies. Training activities in those areas are also deemed important.
12. Implementation of good manufacturing practices (GMPs) is vital and a precondition for conducting BE studies. Consequently, it is necessary to first work with GMPs and adequate controls of active pharmaceutical ingredients (API), moving on later to BE work.

I. OPENING

- Dr. Daniel López Acuña, Director of the Division of Health Systems and Services Development (HSP), welcomed the participants and said that international organizations such as WHO and PAHO/WHO have a stake in and are committed to strengthening all aspects associated with medicinal drug quality and support efforts aimed at guaranteeing a high quality, safe, and effective drug supply. PAHO/WHO and WHO/Headquarters have taken on the challenge of improving access to antiretrovirals and other drugs, as well as ensuring that medicinal drugs acquired by the governments and international agencies meet the required quality standards. He pointed out that priority has been given to actions targeting antiretroviral drugs due to the serious worldwide public health problem.

Dr. López Acuña stated that PAHO/WHO could not be effective working alone on this effort, hence the need to develop strategic partnerships with regulatory authorities, industry, academia, and consumers. Accordingly, PAHO/WHO is coordinating actions with national health authorities to strengthen the regulatory field that guarantees drug quality and is shoring up a system to pre-qualify drug suppliers. To this end, sharing PAHO/WHO and WHO/Headquarters experience is important. Such is the case of the Revolving Fund for Strategic Public Health Supplies, which provides countries with a low-cost option to purchase quality drugs and other strategic supplies jointly. It is also important to share the experiences of WHO/Headquarters on the pre-qualification project and to obtain feedback from the national regulatory authorities so as to plan the next steps.

- Dr. Lembit Rägo discussed the decision taken at a recent meeting of the Expert Committee on the Selection and Use of Essential Medicines to include antiretroviral drugs in the WHO Model List of Essential Medicines (which, incidentally, had just celebrated its 25th anniversary). Dr. Rägo pointed out that the purpose of this workshop was to share experiences on the pre-qualification project, which has helped focus more attention on the quality of pharmaceutical products. The project has two objectives. The first short-term objective is to improve the quality of antiretroviral drugs through quality assurance activities, while the second long-term objective aims at learning about and examining the pre-qualification conditions being developed by national regulatory authorities, NGOs, and international organizations.

Dr. Rägo reported that WHO's experience has led to the development of guidelines for the pre-qualification of multi-source (generic) drugs. He pointed out that, ordinarily, the quality aspects of these drugs are not widely addressed. Consequently, there is a need to develop a quality assurance system that is geared towards harmonization. He noted that antiretrovirals are of great interest at every level and that WHO had tried to put them in the technical area. Drawing on the lessons learned during implementation of its antiretroviral drugs pre-qualification project, today WHO is uniquely positioned in the areas of generic drugs and quality assurance. Accordingly, WHO invites member countries to tap into and learn from this body of experience.

II. PRINCIPLES AND EXPECTED RESULTS OF THE PRE-QUALIFICATION PROJECT: *Dr. Lembit Rägo*

Dr. Rägo began his presentation stating that the drug pre-qualification project was launched as a result of the request from countries and other organizations to help ensure the quality of drugs, specifically of a technically complicated group of drugs, as well as from many UN agencies that lack technical knowledge. Partners of this project are UNAIDS, UNICEF, WHO, and UNFPA, with support from the World Bank. The project is considered a global initiative within the framework of the International Pharmaceutical Coordination Group (IPC), a biannual forum that brings together representatives from UNFPA, UNICEF, UNAIDS, WHO, and the World Bank, as well as other organizations. Aware of the need to guarantee drug quality, an agreement was reached to launch the project with the drugs used to treat priority diseases: AIDS, malaria, and tuberculosis. Thus far, the project has targeted antiretroviral products, but is soon expected to branch out into other areas.

The project has two main objectives: First, to evaluate the quality of products associated with HIV/AIDS (pre-qualification), and second, to create a WHO model quality assurance system for drug procurement. Consequently, several items were identified, including the building blocks process for setting up a quality assurance system. The first draft of the Model Quality Assurance System (QAS) was created with that instrument. The same process is expected to work towards harmonization through the QAS. The step-by-step approach was implemented with several parallel activities: creation of the internal WHO/QSM Quality Assurance System; creation and implementation of the Manual for Standard Operating Procedures; and development of general procedures for drug pre-qualification and a Quality Manual.

A relatively large number of products and suppliers were reviewed, and during the implementation phase, some problems and deficiencies were identified. Those problems included the fact that several substances and products were not in pharmacopoeias. There was also unacceptable chiral activity and stereoisomerism, and unacceptable impurities. The lack of reference standards was identified as a significant problem, as well as the lack of analytical methods and method validation. In conclusion, it was agreed that national regulatory authorities do not follow WHO recommendations for product registration and that regulatory approval in general is not based on evaluations.

With regard to the Active Pharmaceutical Ingredients (APIs), incomplete data and information were common, especially those related to the route of synthesis and supplier, validation of analytical methods, stability data of both API and finished products, process validation, development of pharmaceuticals, and bioequivalence.

The more common good manufacturing practices (GMP) deficiencies are: manufacture in the same area as hormones, cytotoxic, and ARVs; lack of qualification and validation (premises, systems, equipment, and processes); lack of cleaning validation and of verification of air classification in sterile product manufacturing areas. There was no sampling and testing of APIs, while there was a loss in the traceability of materials used in production. Fraudulent data was also found in the process.

Some results indicated that the first list of pre-qualified suppliers already appears in the WHO web page, and that more products and suppliers would be on the list by the end of

2002. It is important to point out that suppliers are willing to improve, knowing that quality assurance has a price. Through this project, it was also possible to obtain a unique knowledge about ARVs.

Finally, some challenges were identified with respect to drugs other than those used in the treatment of HIV/AIDS. The step-by-step harmonization of Quality Assurance Systems in procurement organizations demands a long-term commitment. It also demands mutual trust among those who start using the QAS exchange for inspection results and other information, which will result in less duplication and a common pool of pre-qualified products as public goods.

III. GENERIC DRUG POLICY IN BRAZIL: Dr. Silvia Storpitis

Dr. Storpitis indicated that Brazil has prioritized implementation of a generic drug policy. Part of that policy includes the assurance of the quality of generic drugs, aimed at ensuring their interchangeability. Accordingly, emphasis was placed on required bioequivalence studies as a means to determine interchangeability, and on the importance of validation using analytical methods. With respect to generic drug policies implementation, Brazil has an office on generic drugs, with specialized functions and a specific procedure for the approval of these products. Generic products represent a challenge, with a number of hurdles that must be overcome if the Brazilian market for these products is to be expanded.

Bioequivalence studies and laboratory operations are strictly regulated. Numerous pharmacy schools are capable of conducting bioequivalence studies. If a company wishes to register the drug as a generic, it must abide by all regulations, meet pharmaceutical equivalence and bioequivalence standards, and adhere to good manufacturing practices.

In Brazil, products are classified into three categories: reference (innovative), generic, and similar products. At present, a significant number of similar products are in the Brazilian market that will eventually have to comply with a set of regulations currently under review and which include bioequivalence.

Brazil does not place constraints on the registration of patented drugs; however, intellectual property is respected. Two institutions are involved in the patent process: the National Institute of Industrial Property (INPI) and the health authority, which reconfirms the decision. Patents are not viewed as a health requirement, but rather as a commercial requirement.

IV. WHO BASIC PRINCIPLES FOR GENERIC DRUG REGISTRATION: Dr. Lembit Rägo

With respect to generic drugs, Dr. Rägo pointed out that WHO has specifically acted in accordance with the provisions of the Model List of Essential Medicines. However, limited standards have been set with regard to drug safety and efficacy. With respect to drug efficacy, good clinical practice (GCP) guidelines have been developed and are currently under review, taking into consideration other available standards, such as

those developed by the International Conference on Harmonization (ICH). WHO has focused primarily on drug quality during the post-marketing phase.

In 1999, WHO prepared the *WHO Marketing Authorization of Pharmaceutical Products with Special Reference to Multi-Source (Generic) Products: A Manual for a Drug Regulatory Authority*, a document known as the “blue book,” which is available on the WHO web page.

V. EVALUATION OF LICENSE APPLICATIONS TO MARKET GENERIC PRODUCTS: Dr. János Pógany

Dr. Pógany presented all the quality criteria associated with evaluating license applications to market multi-source (generic) drugs. He noted that a comprehensive technical definition of pharmaceutical quality refers to the product’s fitness for use, and that this should be legally enforced. Quality starts from the manufacturing authorization, which includes design, construction, authorized person, and manufacturing. It refers to GMP according to official compendia, national legislation; and inspection, which involve quality control, IPC adjustment, validation re-qualification, and stability. Quality in marketing authorization refers to the development of pharmaceuticals, their prospective validation, and accelerated stability, among other factors. Quality should be based on defined criteria for its evaluation, many of which have been developed by WHO and other agencies (*i.e.*, FDA and ISO standards).

Dr. Pógany pointed out that WHO recommendations on drug quality often differ from those of individual countries, a difference that may have international trade implications. The principal criteria for pharmaceutical quality are (i) safety, (ii) efficacy, and (iii) good consistent quality. WHO contributions to the preparation of technical documents and guidelines for all these aspects are being widely applied. The basic criteria for evaluating applications to market multi-source (generic) products are well described in the WHO publication known as the “Blue Book”. However, it is important to point out that the requirement that most needs to be fulfilled is (iii) above: quality has to be consistent and acceptable. Products should be interchangeable with pharmaceutical equivalents in the same markets and accurate, using local product information. The three requirements are necessary to ensure quality safety and efficacy.

Dr. Pógany further discussed the basic criteria for evaluating applications to market multi-source (generic) products, including local and foreign drug manufacturers and raw materials. He explained that there are several options available in evaluating applications for well-established products: (a) the national drug regulatory agency (NDRA) prepares its own report (or comments on experts’ report); (b) the NDRA relies on decisions made by other NDRAs; and (c) a combination of these options. However, an evaluation must be conducted if the report or a decision is not available from other NDRAs.

Evaluation of data on quality includes test methodology, impurity, API manufacturing sites, stability data, and container labeling. Even though very few countries regulate pharmaceutical products for export, the same standards should be applied to imported and locally manufactured products. The NDRA must evaluate products developed and

manufactured domestically. If the product is developed abroad, the NDRA may rely on the decision and/or evaluation made by the foreign DRA; in this case, a WHO-type certificate should be issued. For imported products, if the decision is based on a marketing authorization by a foreign NDRA without a WHO-type certificate, the key issues to consider are: batches should be of the same quality, same manufacturer, same API supplier, and sample tested, and a product-specific GMP inspection should be required.

Regarding the quality of starting materials (APIs), it is important to be consistent, with an official and internationally recognized pharmacopoeia. Even though a supplier's certificate of analysis is acceptable, each container's contents must be identified. And compendial testing is recommended if the supplier is different from the producer and if the producer's analysis reliability has not been evaluated.

The container labeling must include the product name, batch numbers, status of the content, and expiration date or re-testing date. Toxicological, pharmacological, and clinical data can be summarized, except when there is a new indication, new patient population, new fixed-ratio combination, or if the safety-efficacy balance is in doubt. In this case, the therapeutic equivalence should be evaluated. Product information must show that the NDRA agrees with the indications, patient population, contraindications, etc. Product information should be defined by law and made available to the public. An expert advisory body is always recommended for local circumstances and endemic diseases.

Standard conditions should be appended for marketing authorizations, and a periodic review is essential. Revocations and suspensions of marketing authorizations should be implemented.

WHO guidelines ensure safety, efficacy, and consistently good quality of multi-source drug products, thus their implementation in national legislation has a significant impact on harmonization.

VI. PHARMACOPEIAL MONOGRAPHS AND REFERENCE STANDARDS: Dr. Myriam Mehmandoust

Dr. Mehmandoust reviewed the concept of pharmacopoeia as a compendium containing standards, norms, and analytical tests describing the quality of pharmaceutical preparations and their components: active pharmaceutical ingredients (APIs), excipients, and packaging. She mentioned the major reference pharmacopoeias as USP, Ph European, Ph Japan, and International Pharmacopoeia (IP). IP considers the needs of developing countries, giving priority to those drugs in the WHO Model List of Essential Medicines, as well as products used in public health to control priority diseases such as HIV/AIDS, malaria, and tuberculosis.

Dr. Mehmandoust also described how a pharmacopoeial monograph is prepared, emphasizing that each pharmacopoeia has its own procedure for elaborating a monograph before publication. However, all monographs follow the basic principles of verification of analytical methods by several laboratories and extensive consultation of experts, manufacturers, and licensing and control authorities.

She defined the Reference Standards “authentic specimens approved as suitable for use as comparison standards in certain tests and assays to achieve the accuracy and reproducibility of analytical results required in a pharmacopoeial context.”

Dr. Mehmandoust stated that for APIs not described in pharmacopoeia, a Reference Standard must be available. She cited specifications for active ingredients and finished products, with emphasis on antiretrovirals. As an example, she mentioned the case of Saquinavir, which has 64 possible stereoisomers; nevertheless, the pharmacopoeias include monographs for only one. About 99% of registered products regularly refer to the monographs appearing in pharmacopoeias.

The absence of pharmacopoeial monographs represents one of the difficulties in evaluating the quality of antiretroviral drugs. WHO has used various strategies for joint collaboration with institutions responsible for the pharmacopoeias in order to move forward with the preparation of monographs. Drug manufacturers also have been required to cooperate in this endeavor, but have not always been forthcoming.

Drug quality guidelines have been developed mostly for multisource (generic) pharmaceutical products. Quality standards for most of these products are specified in major pharmacopoeias.

She mentioned that Lamivudine, Stavudine, Indinavir, and Nevirappine were products for which there are no well-established APIs. Some of the specific problems were: lack of information on the stereochemical configuration on the manner the synthesis can lead to the correct enantiomer, lack of validation on the API manufacturing process, lack of limits, and lack of appropriate control test for the undesirable enantiomer. She concluded that the outcome of the first round of the evaluation exercise was that the data submitted was insufficient and, consequently, quality was not demonstrated.

She highly recommended updating WHO guidelines to give clear guidance on the complex aspects of not well established, non-compendial APIs, and exploring if WHO requirements are met for products moving into international markets under the WHO-type certification scheme.

VII. WHO GUIDELINES ON BIOEQUIVALENCE: Dr. Conrad Pereira

Dr. Pereira’s presentation considered the following questions: Why is bioequivalence necessary? What are the best methods to demonstrate bioequivalence? In which cases are bioequivalence studies necessary and in which unnecessary?

He noted that pharmaceutical equivalence does not necessarily mean therapeutic equivalence, and that multi-source drug products should conform to the same standards of quality, safety, and efficacy required of the reference product and must be interchangeable. Differences in excipients or in the manufacturing process may lead to differences in product performance. Also, *in vitro* dissolution does not necessarily reflect *in vivo* bioavailability.

Dr. Pereira stated that the way to demonstrate BE includes comparative bioavailability (bioequivalence) studies; comparative pharmacodynamic studies in humans;

comparative clinical trials, and *in vitro* dissolution tests. However, BE studies are not needed when the multi-source product is either (a) an aqueous solution for parenteral use; (b) a solution for oral use; (c) a gas; (d) a powder for reconstitution as a solution for oral or parenteral use; (e) an optic or ophthalmic solution; (f) a topical aqueous solution, and/or (g) an inhalation product or nasal spray as an aqueous solution. For (e), (f) and (g), formulation of the multi-source product must be similar to the reference product.

He also stated that bioequivalence studies might be waived for compositionally similar strengths when one strength in a range has been studied. On the contrary, BE studies are particularly needed for pharmaceutical products for systemic action such as:

- a) Immediate oral release when one or more of the following criteria apply:
 - i. indicated for serious conditions requiring assured therapeutic response;
 - ii. narrow therapeutic window/safety margin; steep dose-response curve;
 - iii. complicated pharmacokinetics;
 - iv. unfavorable physicochemical properties, e.g., low solubility;
 - v. documented evidence for bioavailability problems related to the drug;
 - vi. where a high ratio of excipients to active ingredients exists;
- b) Non-oral and non-parenteral, such as transdermal patches, suppositories;
- c) Modified release, and
- d) Fixed combination.

Dr. Pereira discussed the design for comparative studies on bioavailability, noting that those studies should be carried out in accordance with GMP, GCP, and GLP. The most common designs are single-dose and randomized two-way crossover studies. However, parallel studies are also possible for drugs with long half-lives, or steady-state studies in patients for some non-linear drugs.

Among the factors to be considered in designing BE studies are: protocol, study formulation, subjects, etc. The assay validation criteria for the study should cover specificity, accuracy, precision, sensitivity, and stability.

The reference product for the study should be a product in which the safety, efficacy and quality are well established, and it is usually the innovator's product. In reference to the modified-release delivery system, there are greater concerns about safety due to the possibility of dose dumping, and it may be more difficult to establish equivalence.

The critical parameters to evaluate bioequivalence studies include suitability of the study, adequacy, and appropriateness of its validation, pharmacokinetic, and statistical analysis.

It was confirmed that pharmaceutical equivalence must be established as a precondition to conduct bioequivalence studies. When a product is bioequivalent to the reference product, it means that it is therapeutically equivalent to it. Multi-source products should meet the same standards of quality, safety, and efficacy, as the reference products do.

Dr. Pereira also clarified that with respect to bioavailability studies of drugs that carry risks for people's health (*i.e.*, cytotoxins), the patients in treatment must be used.

VIII. QUALITY OF ACTIVE PHARMACEUTICAL INGREDIENTS: *Dr. Myriam Mehmandoust*

In her presentation, Dr. Mehmandoust supported that multi-source products must be held to the same standards of quality, safety, and efficacy as all existing products. She explained the WHO definition of pharmaceutically equivalent multi-source products, and noted that products are pharmaceutically equivalent when they have the same amount of the same API, same dosage form, meet the same or comparable standard, and the intention is to administer them by the same route. Multi-source products that are therapeutically equivalent are interchangeable. She also indicated that according to the European Union guidelines, equivalent pharmaceuticals and bioequivalent products are interchangeable, unless there is scientific evidence that safety and/or efficacy differ with respect to the original product.

Later, she approached the subject by focusing on the definition and description of the quality of generic drugs, with emphasis on Active Pharmaceutical Ingredients (APIs). There are two API categories: those described in an international pharmacopoeia with an official reference standard available, and those not described in an international pharmacopoeia, with no reference standard available, for which full data should be provided. Description of the quality of an API should refer to its structural analyses, physico-chemical properties, manufacture (method of preparation), and specifications. WHO requires: (a) Definition (name, INN, nomenclature, formula, mixture of isomers, stereochemistry, etc.); (b) evidence of structure, including stereochemistry, configurational or conformational, (c) elemental analysis, IR, UV, NMR¹H and ¹³C, mass, and crystallography, and (d) physical characteristics, which include appearance, physical state, solid-state properties (polymorphism), solubility, partition coefficients, solution pH, dissociation ratio, particle size, specific gravity, and melting and boiling points.

Dr. Mehmandoust then discussed the relevant aspects considered in the WHO pilot project on drug quality. In the API's first round of evaluation in the WHO pilot procurement project, information on the API manufacture was usually absent and additional information had to be requested. Some additional information was submitted by a finished pharmaceutical products (FPP) manufacturer or directly by an API manufacturer (similar to a drug master file procedure for confidential reasons). Other FPP manufacturers refused to submit information for confidentiality reasons.

WHO guidelines require that information on a GMP application by an API supplier include details on the route of synthesis, to ensure that they lead to the right structure/enantiomer; and should also include an impurity profile to comply with safety issues.

She referred to the acceptability of quality in terms of safety and efficacy, the reproducibility of quality demonstrated by validation; and lastly, the period over which the quality can be maintained based on stability. She noted that to assure batch-to-batch consistency, API specifications must be known, which include proper identity, strength, quality, and purity. Appropriate tests to control relevant impurities are necessary to ensure efficacy and safety, such as enantiomeric purity, and polymorphism (if applicable).

With respect to validation of the manufacturing process (required by the FDA, but not by WHO or the European Union), Dr. Mehmandoust emphasized the identification of critical

points and certain characteristics of the lots produced. Also discussed was validation of the analytical methods. She mentioned considering the degradation of active pharmaceutical ingredients during the reevaluation period, those properties susceptible to alteration during storage, and guidelines for well-established active pharmaceutical ingredients as well as for new antiretrovirals. She cited examples of the parameters measured for antiretroviral drugs included in the WHO-led evaluation, in which the aforementioned parameters were taken into account.

Finally, Dr. Mehmandoust mentioned that with respect to deficiencies, public health is the overriding concern. She also supplied a useful bibliography on the topic.

IX. QUALITY OF THE FINISHED PRODUCT: MULTI-SOURCE AND LIMITED SOURCE: *Dr. János Pógany*

Dr. Pógany reviewed some WHO definitions on finished pharmaceutical products, multi-source (generics) products, and proprietary pharmaceutical products. He noted that well-established finished pharmaceutical products (FPPs) are those that: (a) have been marketed for at least five years in countries that undertake active post-marketing monitoring; (b) have been widely used to permit the assumption that safety and efficacy are well known; and c) have the same route of administration and strength, and the same or similar indications in those countries.

Multi-source (generic) pharmaceutical products are those pharmaceutically equivalent products that may or may not be therapeutically equivalent. Multi-source pharmaceutical products that are therapeutically equivalent are interchangeable.

Finally, he defined oligosource finished pharmaceutical products as those that are available from more than one manufacturer; may or may not be well-established according to WHO criteria, contain an API not yet official in an internationally recognized pharmacopoeia, and require particular attention by NDRAs as regards evaluation of applications for marketing authorization.

Dr. Pógany also reviewed the primary regulatory elements of drug quality in the various stages: production authorization, good manufacturing and inspection practices, and marketing authorization.

Furthermore, he stated that those results cover experience from the evaluation of 124 product dossiers from 18 companies. The major critical deficiencies found in the solid dosage forms of the products examined are those considered CRITICAL, such as a deficiency, potentially leading to a significant risk of manufacturing an API or an FPP which is harmful to the human patient, and those considered a SIGNIFICANT DEFICIENCY, which include a non-critical deficiency, potentially leading to a multi-source (generic) or oligosource API or FPP which does not meet the criteria of essential similarity. A deficiency is also evaluated as SIGNIFICANT if it may result in an FPP that does not comply with its marketing authorization or the GMP requirements as recommended by WHO.

The most illustrative deficiencies are: a) pharmaceutical development and scale-up information, including biobatch data, are not submitted; b) potentially critical API, product and process quality parameters are not studied and are only formally monitored; and c)

stability data on FPPs is unavailable or the analysis is inconclusive. He highly recommended that critical API parameters be part of the purchasing specifications.

Dr. Pógany noted that FPP manufacturers in general accept compendia specifications, without accepting criteria for physical properties described in the literature as critical (crystal form, particle size distribution, and bulk density). With regard to new generic products, the first three production scale batches must be monitored as comprehensively as possible to establish definitive IPC and to test specifications for the marketing authorization. Also concurrent validation should be carried out throughout the life of the products.

On the aspects of the stability tests conducted on active ingredients and of the concurrent validation process, it was noted that: (a) no studies were submitted; (b) there is no evidence that the QC assay and impurity test methods indicate stability (degradant); (c) protocols and reports do not include evaluation of dissolution; and, (d) stability data is not analyzed and does not justify the proposed DRA-approved expiration date.

The main conclusions drawn from the study are: (a) manufacturers of generic drugs rarely follow the WHO Guidelines and are adopting them gradually; (b) there is nothing like a conventional (standard normal routine) FPP manufacturing process; (c) validation IPC tests and stability studies are not formal requirements, and (d) an NDRA plays a key role in the implementation of WHO guidelines.

Finally, he presented some technical details on the evaluation of Indinavir, confirming that the bioavailability of Indinavir is good, which facilitates pre-formulation and formulation research for generic manufacturers. The toxic-pharmacological information suggests that Indinavir pharmaceutical forms may be manufactured in multi-product plants.

It is important to bear in mind that, in some countries, pharmaceutical products tend to be manufactured in two types of plants: one for domestic consumption and another for export. Consequently, it is important to ensure compliance with GMPs and good registration and control practices for raw materials.

Dr. Pógany pointed out the difficulties to determine the true origin or source of raw materials, which tend to be marketed by “brokers in Latin America.” He also indicated that manufacturers do not always provide stability data.

X. EXPERIENCE IN EVALUATING DRUG DOSSIERS IN TERMS OF BIOEQUIVALENCE DATA: Dr. Conrad Pereira

The Project started inviting manufacturers of non-nucleoside reverse transcriptase inhibitors, nucleoside reverse transcriptase inhibitors, protease inhibitors, selected anti-infective drugs, anti-cancer drugs, and drugs for palliative care to express interest to WHO. The requested documentation to demonstrate interchangeability in the case of multi-source (generic) preparations includes bioequivalence studies based on the WHO guidelines. Bioequivalence data is required for oral preparations, except aqueous solutions, at the time of administration. Orally or parenteral administered aqueous solutions will be assessed by chemical-pharmaceutical characteristics only. Also a BE

study was required for preparations indicated for serious conditions requiring assured therapeutic response, which included all formulations in the offered list.

An evaluation of antiretroviral product dossiers for bioequivalence data has been conducted on four occasions, the last one taking place in January 2002. A total of 158 antiretroviral product files were evaluated, 47 (30%) of which involved innovative products and 111 (70%), generic products. Cases that did not require bioequivalence data were excluded. Of the 111 generic products evaluated, 3 were protease inhibitors; 4 were non-nucleotide reverse transcriptase inhibitors (NNTIs); and 36, reverse transcriptase inhibitors (RTIs). The primary conclusions gleaned from the 43 dossiers on generic antiretroviral drugs indicate that only 4 satisfied WHO requirements to demonstrate bioequivalence with the innovative product. There were no bioequivalence studies conducted on 32 files, and no justification was presented in this regard. Moreover, in 14 files, the validation data on the analytical method were inadequate.

Among the major deficiencies found were that there was no BE study performed nor an adequate justification for this (32 files); there was inadequate validation data of bioanalytical method (14 files); and no verification existed to show that the product used in the BE study is identical to the product intended for marketing (13 files). Nine files did not present 90% confidence interval for pharmacokinetic parameters; and a non-assessable comparative efficacy study was found in one file.

Minor deficiencies included information not included but easily accessible, and lack of individual pharmacokinetic parameters, statistical calculations, or detailed descriptions of study designs that were not submitted. Other minor deficiencies included the non-submission of a certificate of analysis of test batch and/or *in-vitro* profile for a test product, reference product, or different strengths of the same product.

One possible reason for this situation is the fact that several generic antiretroviral manufacturers have rushed into the market without meeting the necessary quality assurance requirements. Generally speaking, there is no proof that these products are bad. But, by the same token, there is no proof that they are good either. Dr. Pereira conceded that while a good deal of progress has been made with regard to quality assurance, it is still not enough. He recommended that countries develop a medium- to long-range plan for implementing bioequivalence studies and draw up a list of critical products.

Some regulatory authorities expressed the concern that, while the suggestions made in the presentations are technically speaking of a very high quality, they are not necessarily applicable to many of the generic products marketed in Latin America. It was emphasized that although most of the countries in the Region have real problems, the suggestions should be adapted to real conditions in these countries, since antiretrovirals constitute a critical drug group, owing to the resistance problems that are already emerging.

XI. GMP MONITORING AND WHO PREQUALIFICATION: Dr. János Pógany

After presenting the existing quality systems and differentiating between compulsory and voluntary regulations, Dr. Pógany spoke about the chronological establishment of the WHO guidelines on good manufacturing practices (GMPs). He reviewed the conceptual elements of pharmaceutical GMPs, explaining their structure and principles. He emphasized that WHO guidelines on GMPs are compatible with those of the European Union.

Dr. Pógany described the WHO GMP auditing process carried out in four companies and six manufacturing plants. A team of three inspectors led this audit: one from the regulatory authority, one from WHO, and the team's chief inspector. The examples Dr. Pógany cited were aimed at critical deficiencies in the manufacturing processes of solid dosage forms. The GMP inspection covered infrastructure, equipment, manufacturing processes, and validation methods. With regard to infrastructure, it was found that hormones were produced in the same areas and with the same equipment as cytotoxic and antiviral agents. The sampling area was "old," with evidence of damage and rust. There were also signs of physical deterioration and inadequate maintenance, e.g., top of the door, part of the ceiling joints, and lighting defects.

With respect to the deficiencies observed, Dr. Pógany pointed out that few manufacturers used a reduced sampling plan for raw material quality control. Deficiencies included cross-contamination, since there was no status label indicating the current status (cleaned, in use, products) of the manufacturing rooms. There were also problems with validation, stability studies, and staff training in standard operating procedures.

With regard to work processes in aging manufacturing plants and the pertinent WHO recommendations, these improvements should ideally be carried out gradually, adhering to the technical guidelines. He stated that GMP starts with the design and construction (D&C) of facilities and research and development (R&D) of products and should be continuously improved. He also reminded the participants that validation, pre-qualification, preventive maintenance programs, and annual product reviews are guarantees of batch-to-batch reproducibility and long-term consistency of quality.

He reiterated the need for technical cooperation among countries (TCC), primarily to address the problem of differences between GMPs at the country level and WHO guidelines.

XII. QUALITY ASSURANCE AND THE REGIONAL REVOLVING FUND FOR STRATEGIC PUBLIC HEALTH SUPPLIES: Dr. José María Parisi

Dr. Parisi started his presentation noting that the Regional Revolving Fund for Strategic Public Health Supplies is an initiative launched two years ago at the 42nd PAHO Directing Council. The following product groups were selected for the first phase of the initiative: antiretrovirals, antimalarials, tuberculosis drugs, antiparasitics, and

insecticides/pesticides. Accordingly, there is a need to establish quality assurance for the products purchased.

Immediate actions include the pre-qualification of suppliers. Medium-term actions include implementation of the 1992 WHO GMP guidelines, training of GMP inspectors using modules developed by WHO, establishment of a network of reference laboratories for quality control in the Americas, dissemination of the GMP guidelines for raw materials, and quality assurance in the procurement of drugs.

In the first stage of the program, focusing on quality control laboratories, dissolution tests were conducted and the HPLC methodology was applied. A total of 18 laboratories participated. The results indicated that three of them required technical support.

To date, eight countries in the Region of the Americas have signed agreements with PAHO to participate in the Regional Revolving Fund for Strategic Public Health Supplies.

XIII. CLOSURE

- Dr. Rãgo thanked the participants for their feedback, reiterating his position that there are two types of recommendations: those that can be applied by the countries of the Region and the WHO guidelines.
- Speaking on behalf of Dr. López Acuña, Dr. Caridad Borrás thanked the countries and the representatives from WHO Headquarters (Dr. Rãgo and invited colleagues) for their participation, as well as PAHO/WHO staff who helped make the meeting possible.