RED PARF: Grupo de Trabajo en Bioequivalencia (GTBE)

MINUTAS DE LA 1ra REUNIÓN

Fecha: 14 Septiembre 2001

Actividad preliminar: Estudio diagnóstico de bioequivalencia (FDA)

Actividades asociadas: Taller de AAPS sobre clasificación de Bioequivalencia

Lugar: Administración de Alimentos y Medicamentos (FDA), EE.UU.

Asistentes:

- Justina Molzon, FDA Coordinadora
- Mei-Ling Chen, FDA
- Ricardo Bolaños, ANMAT/Argentina
- Norman Pound, Canadá
- Eugenie Brown, Jamaica
- Roger Williams, USP
- Salomon Stavchansky, Texas
- Mara Nussenbaum de Levy, INH Venezuela
- Silvia Giarcovich, ALIFAR
- Ofelia Espejo González, FIFARMA
- Secretariado: Rosario D'Alessio

Recursos técnicos:

- D. Conner
- A. Dorantes
- L. Sánchez
- J. Jenkis
- J. Cory
- L. Lesko
- A. Sancho
- S. Suárez-Sharp

Observadores:

- Argentina: M. Maito, G. Pesce
- Brasil: G. De Nucci, S. Storpirts, E. Correa
- Chile: R. Pezoa, A. Arancibia
- Colombia: L. F. Ponce de León
- Costa Rica: L. Fonseca, G. Salazar
- Guatemala: A. L. Valle
- México: H. Jung, C. Becerril
- Panamá: V. Turner
- EUA: E. Fefer
- Venezuela: E. Sanabria

Objetivo: Definir la estructura de los programas de adiestramiento

Minutas (Solo en Ingles)

Opening Statement by Rosario D'Alessio.
On behalf of PAHO, I would like to express my gratitude to the FDA for arranging the logistics of this meeting, especially to Justina Molzon. The mission is to develop the training courses in pharmacokinetics, pharmacodynamics and bioequivalence including GMP's, GLP's and GCP's, to be offered in the Americas and a plan of work for the working group to present to the Steering Committee

Opening Statement of Justina Molzon.
Justina delivered an excellent talk reviewing the structure of the Drug Regulatory Harmonization Committees. The first meeting of the steering committee was held in Caracas Venezuela. The steering committee met in Puerto Rico and decided that bioequivalence issues were priority. The bioavailability-bioequivalence work plan has been designed. Part of the objectives is to develop an educational program for the Americas. This program will include pharmacokinetics, pharmacodynamics and bioequivalence concepts. In addition, funding and training sites need to be decided.

Alfredo Sancho presentation.
A survey questionnaire was developed and mailed to the Americas excluding Canada and the Caribbean. Dr. Alfredo Sancho discussed the responses. A handout with the results was handed out to the participants of the meeting. Argentinean representatives stated that the regulatory agency is in transition and this explains the reason that no answer was received from Argentina. Approximately 50% of the countries stated that they have laws that require BA-BE studies. Training is a weakness in several countries and all countries stated that they would like to have training courses,
In addition, (number in parenthesis is the number of reviewers), Venezuela (10), Costa Rica (6), Mexico (30), and Brazil (60). It is not clear if the number reflects actual people or available positions, and/or a combination of both.

ALIFAR also conducted a survey in the Americas and the results are similar to the results of the survey conducted by the FDA-PAHO. There was some discussion regarding the validity of the surveys. However, Rosario D'Alessio suggested that we use the FDA-PAHO survey as preliminary and as a guide for future developments.

The results of the survey overwhelmingly support the development of training courses in the areas of basic principles of bioavailability and bioequivalence, study design, data analysis, data interpretation, and case studies demonstrating the principles discussed in the course. Participants in the training courses would include scientists of the regulatory agencies, academia, and industry.

Mei Ling
The following is the suggested structure for the content of the course.

- **General Considerations**
  - The application Process
  - Terminology and Definitions
    - Drug Substance
    - Drug Product
      - Drug Product Quality

        - USP Standards
    - Bioavailability
    - Bioequivalence
    - Therapeutic Equivalence
    - Therapeutic Alternatives

- **In Vitro Methods**
    - Introduction
        - Utility of Dissolution in Quality Control and BA-BE Waivers.
    - In Vitro Dissolution
        - Dissolution Methodology
            - Practical Aspects and Case Studies
                - Immediate Release Dosage Forms
                - Controlled Release Dosage Forms
            - Use of surfactants
            - USP Dissolution Apparatuses
                - Importance and utility of each dissolution method
                - Factors affecting dissolution
        - Analytical Methodology
            - Theoretical consideration
            - Validation, specificity, sensitivity, accuracy, precision, etc.
            - HPLC-MS and HPLC MS-MS
        - Dissolution Profile Comparison
            - Single point specification
            - f2 and bio-waivers
        - In Vitro-In Vivo Correlation
            - Deconvolusion

    - BCS
        - Introduction
            - Solubility
            - Permeability
        - Link of in vitro dissolution and BCS

- Post-training experiences in Regulatory Agencies

- **In Vivo Methods**
    - Clinical Trial Protocol
        - The Reference Product
        - Final FDA BA-BE guidance
        - WHO guidance
    - Assay Method Validation
        - Methodology and Instrumentation
            - Experimental Protocol
                - Limit of Sensitivity
                - Limit of Quantitation
                - Linearity

        - Accuracy
        - Precision
        - Robustness
        - Re-assay of samples
    - BA-BE Waivers
        - High versus low strength
        - SUPAC
    - Training

- **What is Bioequivalence**
    - Purpose of bioequivalence studies
        - Average Bioequivalence
        - Population Bioequivalence
        - Individual Bioequivalence
    - The Reference Product
        - How to select the reference Product
    - Statistical Considerations
            - Bioavailability metrics
                - Variance considerations
                - Methods for declaring bioequivalence
        - Experimental Design of Bioequivalence Studies
            - Parallel
            - Crossover
            - Non replicated
                - Sequence effects
                - Subject(seq) effect
                - Formulation effect
                - Period effect
                - Carryover effect
                - Residual

- **Data Analysis and Reporting**
    - Statistical Analysis
        - In Vitro
            - f2 dissolution
                - In Vivo Sequence effects
                - Subject(seq) effect
                - Formulation effect
                - Period effect
                - Carryover effect
                - Residual
                - When do you change the goal post
                    - Highly variable drugs
                - Non-Linear Kinetics
                - NTI's

- **Pharmacokinetic Software**
  - SAS
  - WinNonlin
  - SPSS
  - Canadian Subroutines are available but need to be validated.

  - **Special Dosage Forms**
    - Cytotoxic Products
    - Nasal
    - Hormones
    - Topicals
    - Meter Dose Inhalers
    - Others

- **Report Format**
  - OGD website has an electronic filing format document to facilitate the submission process.
  - ICH
  - WHO, Quality Assurance of Pharmaceuticals.
  - Canada

- A list of WHO Guidances related to Drug Product Quality and Bioequivalence already exists and will be provided to member countries through PAHO

After the presentation all participants (observers and members) were asked to send their comments on the proposed guide for BE seminars presented by the FDA. A plan of courses or seminars to be held at national or sub regional level was also requested from all participants. It was recommended to send all information via e-mail to PAHO (Rosario D'Alessio) before the end of October. The FDA would consider all comments and PAHO would consolidate all plans.

Tele conferencia (6 Agosto 2001)

Participantes:

- Justina Molzon FDA, Coordinadora
- Alfredo Sancho, FDA
- Norman Pound, Canadá
- Roger Williams, USP
- Silvia Giarcovich, ALIFAR

Secretariado: Rosario D'Alessio

Observador: EUA: E. Fefer

Objetivo: Examinar el trabajo realizado en los módulos de adiestramiento y planear la segunda reunión