RED PARF: Grupo de Trabajo en Bioequivalencia (GTBE)

MINUTAS DE LA 2da Reunión

Fecha: Diciembre 3-4, 2001

Actividad asociada: Primer seminario sobre Bioequivalencia (post-reunión)

Lugar: Caracas, Venezuela

Asistentes:

- Justina Molzon FDA, Coordinadora
- Alfredo Sancho, FDA
- Ricardo Bolaños, ANMAT/Argentina
- Eugenie Brown, Jamaica
- Roger Williams, USP
- Salomon Stavchansky, Texas
- Irene Goncalves, INH Venezuela
- Silvia Giarcovich, ALIFAR

Secretariado: Rosario D'Alessio, Sabine Koop-Kubel
Recursos técnicos: S. Suárez, L. Sánchez
Observadores: Chile: A. M. Concha

Objetivos:

- Desarrollar una propuesta sobre los criterios para priorizar los estudios de bioequivalencia en los países donde actualmente no se hacen
- Elaborar una propuesta sobre los criterios para seleccionar un medicamento como patrón de bioequivalencia.
- Elaborar una propuesta sobre los indicadores que serán usados por el WG/BE para vigilar la aplicación de las normas de bioequivalencia en las Américas.

Minutas (solo en ingles)

Day 1: December 3, 2001

1. PAHO Welcome

2. Coordinator (Justina)—overheads
   Justina welcomed group and introduced attendees
   PAHO (Rosario)—PPT
   Rosario provided an update of PANDRH activities and objectives and discussed the activities of the various Working Groups:

   - GMPs—several workshops, Spanish translations, need for indicators. Justina noted the GMP Working Group has not met.
   - BA/BE—for further discussion

- GCPs—one meeting in Orlando, second meeting November 1 (Guatemala), considering ethics committee, informed consent, development of two year work plan.
- Classification—Mexico in charge
- Counterfeits—first meeting, coordinator ANVISA, meeting December 6—7, 2001
- Good Pharmacy Practice
- Pharmacopeias, met November 20, with many activities. Also associated with regional assessment of ODQCLs, jointly with USP and QSM/WHO. Two years/ four phases, any country with laboratory, check samples, other activities.
- Regional Entity—PAHO/VEN working with Temple University November 2001 and February 2002 (Chile, Argentina, Guatemala, Venezuela, Brazil)

3. BA/BE Working Group
Justina provided an update of WG activities and presented possible areas for discussion -overheads
Topics selected by Steering Committee
Bioequivalence Work Plan (**Bold=** accomplished)

- **Assessment of BE**
- **Selection of team members**
- **Consolidation of questionnaire**
- **Selection of materials**
- **AAPS Workshop (September 2000)**
- Regional Seminar
- Evaluation
- Pending Possibility
- National Seminars
- Regional Seminars
- **Working Group meetings**

Review of meetings:

- Planning Group with Working Group: September 14, 2000

- First meeting of Working Group: September 14, 2000
Focuses on training by modules, with Spanish translation. December 5-8 will focus on Modules 1 and 2. Congratulations were extended from ANMAT/Ricardo on the training materials.

- Steering Committee meeting March 23-24, 2001: report by BA/BE Working Group (Justina/Alfredo)

- Courses: Venezuela (December 2001), Costa Rica (February 2002), Argentina (March 2002). General approach: two professors, several FDA reviewers, local experts and academic institutions, four-day course, 20-30 participants, taught in Spanish, offered once in all sub regions, with second cycle follow-up if needed. One will be taught in English for Caribbean. Goal is to train to standards and then to harmonize—training then becomes an instrument of harmonization.

- Next steps:

  - Analysis of current issues
  - Examine existing regulations
  - Identify differences or gaps
  - Set up action plans
  - Collaboration with other countries
  - Developed harmonized instruments

4. Topics for Discussion

Criteria for prioritizing BE studies in countries where they are currently not being done.

- Indicators to be used by the WG/BE to follow up the implementation of BE in the Americas.
- Criteria for selecting BE drug comparator.

Available documents: 1) WHO 2) FIP—much science agreement based on ten years of discussion at biyearly meetings (Bio-Internationals). It was noted that BA/BE was not discussed in the context of ICH.

Within the Americas there are many areas where harmonization can occur.

- Biowaiver of in vivo BE studies using dissolution
- Number and demographics of volunteers in BE studies
- Study design and need for fed BE studies
- BE limits and confidence intervals
- International reference standard

Discussion of Topic 1: Criteria for prioritizing BE studies in countries where they are currently not being done. (If one is needed and if so, then what kind of study (PK or dissolution) is needed).

Sabine reviewed the WHO document entitled *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (Annex 9). The document provides a comparative list based on three countries (US, Canada, Germany) and focused on essential drugs. An additional document (two years old) provides information on comparator products. It is still in editing and will be published shortly (summarized briefly in article provided in PAHO handout).

WHO is continuing a scientific analysis of BCS and associated topics in FIP (Special Interest Groups (SIGs)--BA/BE (Chair: Vinod Shah/FDA). FIP is considering various studies on how to classify permeability of active ingredients. Sabine noted that Expert Committee on Specifications for Pharmaceutical Preparations had recently endorsed work. Focus of this effort should be on classifying ingredients/products that are on the Essential Drug List. Work will continue over the next several months, focusing on Class I drugs.

With above discussion in mind, WG considered *WHO Multisource*...document on page 122. This section lists products for which BE <u>are not</u> necessary. Sol noted that topical and oral inhalation/nasal drug products require special considerations. Group agreed to this with FDA noting that guidances on these documents were in development.

Silvia noted that special considerations would be needed in Latin American countries. Roger spoke about decision tree with further discussion of branches as to whether vivo or in vitro BE studies are needed given that an in vivo study is needed. This is considered on page 123 of WHO document. Group focused on excipients, relying only on dissolution and solubility (not permeability). Sol suggested: solubility/dissolution/ excipients ok, disease state, and NTR drugs. He also mentioned FDA/AAPS document on CD-ROM entitled Pharmaceutical Excipients 2000 (FDA and AAPS). Group also considered expanding relationship with FIP BA/BE SIG (Vinod Shah). Ana Maria Concha noted that Chile intends to follow the WHO/not FDA approaches, with emphasis on high risk (e.g., NTR) drugs. Ricardo noted that when concentrations outside the therapeutic window cause ADR/death, this is high risk. Medium risk is when level falls below therapeutic window, then disease gets worse. Low risk is when concentration is outside range and disease just continues. Silvia noted processes that led to conclusions.

Group then considered how to define risk (life-threatening in terms of ADRs, prolonged hospital stay, induces cancer). Group could propose definition for risk either in terms of being too high (safety) or too low (efficacy). Added to this could be some aspects of the BCS (solubility, rapidity of dissolution). Sol also noted need for first pass considerations, steepness of dose-response curve. Silvia suggested: a) start with EDL list; b) go to smaller list: NTR drugs only. She further noted that Argentina, Brazil, Chile had produced their own lists, based on various considerations—all relative to factors described in WHO document.

Justina summarized two general approaches: 1) when a BE study is not needed; 2) when a BE is needed. These lists were generally put in place in 1996 in the WHO document and perhaps needs to be updated. Goal would be able to focus on NTI and drugs used to treat serious or life-threatening illnesses.

Summary:

Starting with 1996 list in WHO document, focus can be on immediate release products where three countries (US, Canada, Germany) all agreed on need for in vivo study. Starting with this list, then supplement with lists from Chile, Argentina, Venezuela to see which are high risk drugs where in vivo BE studies are needed. Union of four 'lists' will result in high risk and NTR drugs. Drugs coming into market after 1996 will not be considered at this time.

Over lunch time, Sol and Roger worked on the lists according to the general approach. This resulted (with Brazil's list) in a group of approximately 50 active ingredients that could be considered high risk/NTR and for which in vivo BE studies would be required. This list could be combined with the BCS approach (not highly soluble, not rapidly dissolving, problems with excipients) to come to a list of prioritized drugs where in vivo BE studies would be needed. This would correspond to a clarification/adaptation of the WHO approach on page 123 of the *Multisource* document.

Discussion of Topic 2: Criteria for selecting BE drug comparator.

Sabine opened the discussion with a review of the WHO document, which summarized general approaches to determining pioneer drug. Irene noted challenges of determining local 'pioneer' is the same as the 'pioneer' product on which safety and efficacy is based. Also, local and/or international pioneer product may have changed in terms of its performance. Roger provided example from Dr. Lugones/ANMAT for oxycarbamazepine, where specific, validated RLD had been identified. Silvia noted need for two-stage process: 1) validation of reference product, 2) then conduct pioneer to generic study. Silvia noted

that pioneers sometimes don't pass in vitro dissolution. This had been problematic because no national laboratories wanted to study pioneer/generic products in vivo if the pioneer was failing in vitro. This finding led to need to validate pioneer product. Ricardo noted that regulatory authority should have option of dictating which product is comparator. Further discussion occurred on challenges of determining that national pioneer product could be validated. Sol noted that GMP differentials needed to be taken into consideration, also that performance of some pioneer products could be shown to be different in terms of performance. Justina emphasized the need for a pioneer to validate that performance of a reference product was the same throughout the Americas. After pioneer product could be documented—the local manufacturers could be brought into conformance in terms of compliance. Justina pointed out need for equal burden in terms of challenge. Also, it would be much more efficient to ask each company to confirm equivalent quality and performance, rather than ask each regulatory agency to validate with pioneer. Also approach would help countries where pioneer no longer markets. Overall very positive effects could accrue to innovator based on several arguments: FTAA, improving quality approaches demonstration of equivalent product quality throughout Americas (if true).

Summary

PAHO could consider sending letter to pioneers based on list of approximately 30 high risk drugs where BE studies are considered especially important. This letter could be based on WHO letter, with additional motivators (quality, PANDRH, FTAA, other). Steering Committee and Conference endorsement will be especially helpful. Rosario noted that letter could be endorsed by a seven member SC prior to meeting via e-mail if WG thought this important. WG thought this was good idea, with goal of draft letter from Justina/Rosario generally approved by WG in January 2002. Rosario thereafter could forward to SC by email for approval. Goal would be to have final letter by end January. Thereafter a letter could be written, using WHO mailing list. Note: some gaps probably exist.

Justina noted need to continue with validation approaches, assuming primary approach to identify RLD (previously discussed) was not successful. Approaches include those of Canada and WHO. General process can be referred to as validation.

Group then returned to a discussed of how to 'straighten out' past markets when BE was not required. Focus in this setting might be on dissolution as a means of showing BE and avoiding the need for in vivo BE studies. Goal might be to have optimally performing local products (e.g., good excipients, highly soluble, rapidly dissolving) be declared to be bioequivalent based on suitable comparisons to a reference products. Sandra noted that f2 comparisons might be needed where dissolution as between 15 and 30 minutes, per the FDA BCS document. End result might be rapid way to straighten out 'past' of a market, recognizing that many in vivo BE studies would not be performed.

Topic #3: Indicators to be used by the WG/BE to follow up the implementation of BE in the Americas.

Justina led discussion of indicators. Focus should be on how to document advances in progress of network. Primary question yields set of indicators. Group also considered idea that there could be 'Americas Orange Book' that would yield information about BA/BE, method of BE, GMP, specifications, etc. Ana Maria Concha noted possibility of adding numeric value or rating to make questionnaire more quantitative and less subjective. Goal will be to look for changes. Rosario emphasized important it is to know that countries are using results of PAHO effort.

Day 2:

Based on the discussions of the first day, the second day of the Working Group's meeting was spent developing proposals to be submitted to the PANDRH SC for consideration at the III Pan American Conference on Drug Regulatory Harmonization, 24-26 April 2002.