Scientific Advisory Panel on Bioequivalence Requirements for Gender-Specific Drug Products (SAP-GSDP)

Teleconference
Record of Proceedings
June 2, 2011

Panel Members: Jake Thiessen (Chair), Robert Herman, Elaine Jolly, William Racz, Heather Shapiro, Daniel Sitar, Scott Walker

Health Canada Representatives: Supriya Sharma, Therapeutic Products Directorate Team

Welcome and Opening Remarks from Director General (S. Sharma, Therapeutic Products Directorate)

The Director General opened the meeting by welcoming the members and introducing Health Canada representatives through a formal roundtable. Dr. Sharma indicated that the members will be consulted on issues concerning appropriate bioequivalence study requirements for pharmaceutical drug products intended for gender-specific administration. Specifically, the questions posed to the panel members will revolve around the requirements for inclusion of males only, females only, or males and females in bioequivalence trials for products that are intended for use in pregnant women. Dr. Sharma thanked all panel members for their time and effort in participating in this meeting and wished everyone good and productive deliberations.

Chair's Address (J. Thiessen)

The Chair welcomed the panel members.

The Chair gave a brief overview of Health Canada's processes and policies revolving around bioequivalence requirements. He informed the panel members that Health Canada has asked for the panel's expert advice regarding any specialized requirements for a second entry or subsequent entry gender-specific drug product to acquire market authorization in Canada. Specifically, the panel is to answer the three questions posed to them contained in Tab 4 of the binder sent to them.

Acceptance of Terms of Reference and Conflict of Interest Declaration

The Chair asked the panel members whether there have been any changes in their affiliations and interests since they were last declared to Health Canada. Upon confirmation of the declarations, it was unanimously agreed that all members could participate fully in the meeting and the Chair encouraged free and open discussion.

The Chair asked for any comments regarding the Terms of Reference. All panel members accepted the Terms of Reference as is.

Discussions Regarding the Mei-Ling Chen Report (All Members)

The Chair asked for comments on the Mei-Ling Chen publication which analysed studies submitted to the FDA which contained both males and females. The paper contained gender analysis of intra-subject variation, relative mean area under the curve (AUC) and maximum observed concentration (Cmax.)

Members noted that the studies presented in this paper were small and not designed to address the question of whether or not a gender by formulation interaction exists. The panel suggested that while there might be differences due to gender, in a crossover study when formulations are compared in the same subject, these differences are negated or minimized. The panel members agreed that this paper, on its own, presents no compelling evidence to warrant a gender specific study in bioequivalence testing.

Discussions Regarding the Gideon Koren Editorial (All Members)

The Chair requested comments from the panel regarding the Gideon Koren Editorial. The panel members noted that this editorial does not apply to issues in bioequivalence but rather focuses on other issues, some of which are used in the determination of bioequivalence. Members supported the article's premise that pharmacokinetics of drugs are different in pregnant women than in men, however, this difference is not applicable to the assessment of comparative bioavailability using a crossover design.

[redacted]*

[redacted]*

[redacted]*

*Scientific and proprietary information redacted as per Access to Information (ATI) Act s. 20(1)

Deliberation on the questions posed (All members)

Health Canada posed the following questions to the panel for their considered opinion:

1. *Given that bioequivalence studies are generally intended to verify the performance of a new formulation relative to a reference formulation, and the characteristics of the drug substance itself are already known, it is acceptable for bioequivalence studies, in support of generic version of doxylamine succinate 10 mg plus pyridoxine hydrochloride 10 mg, to be conducted in any of the following:*
   (a) Only males;
   (b) Males and females; or
   (c) only females?

   On the basis of the evidence provided, the panel supported the continuation of the current practice of using only males, males and females or only females for bioequivalence studies. For the specific case of doxylamine succinate 10 mg and pyriodoxine hydrochloride 10 mg, the panel recommended that the current practice of Health Canada to accept bioequivalence studies in only males, males and females or only females is acceptable.

2. *If, in your opinion, bioequivalence studies for this product should be conducted only in women, should these studies be conducted in pregnant women?*

   The panel members unanimously agreed that bioequivalence studies for this product should not be conducted in pregnant women.

   Members established that there is currently no compelling scientific evidence to suggest that the gains from a bioequivalence study on pregnant women would outweigh the risks. The panel members concluded that no ethics committee would agree to putting a pregnant woman at risk (e.g., blood draws) without substantial evidence that the scientific merits from such a study would be beneficial.

3. *Other than the safety of subjects, are there any circumstances where bioequivalence studies should be conducted in a gender-specific sample only?*

   Panel members stated that cases certainly exist where bioequivalence studies do not require gender-specific samples, however, because of the nature of certain drugs; gender-specific samples are used (e.g., oral contraceptives). The members agreed that from a pragmatic standpoint, bioequivalence studies are occasionally done in gender-specific samples; the members acknowledged that Health Canada's current bioequivalence guidance already allows flexibility to accommodate these cases.

   Members emphasized that by definition, bioequivalence revolves around how the generic formulation performs compared to the innovator formulation and this information can be gained from any subject regardless of gender.

The panel made the distinction between examining drug concentrations versus drug effects. If bioequivalence of a gender-specific drug is based on pharmacodynamic studies, the gender of the population employed becomes a more critical consideration.

In conclusion, while the panel does not view the issue as closed, presently there is no compelling scientific evidence to warrant gender-specific bioequivalence studies.

Chair's Closing Remarks (J. Thiessen and S. Sharma)

The Chair thanked panel members for their participation and effort and also to all Health Canada personnel.

Dr. Sharma concluded that the discussion had been very productive and thanked the panel members for their valuable time.

The meeting was adjourned.

References:

1. Koren G. Is it appropriate to study the pharmacokinetics of drugs aimed at pregnant women in men? *J Obstet Gynaecol Can* 2010 Jul; 32(7): 629-32.

2. Guidance for Industry: Conduct and Analysis of Bioavailability and Bioequivalence Studies – Part A: Oral Dosage Formulations Used for Systemic Effects (1992)

3. Guidance for Industry: Conduct and Analysis of Bioavailability and Bioequivalence Studies – Part B: Oral Modified Release Formulations (1996)

4. Chen M-L, Lee S-C, Ng M-J, Schuirmann DJ, Lesko LJ and Williams RL. Pharmacokinetic analysis of bioequivalence trials: Implications for sex-related issues in clinical pharmacology and biopharmaceutics. *Clin Pharmacol Ther* 2000; 68(5): 510-21

5. _____*

*Scientific and proprietary information redacted as per ATI Act s. 20(1)