Johnson & Johnson
PHARMACEUTICAL RESEARCH
& DEVELOPMENT
DIVISION OF JANSSEN PHARMACEUTICA NV

August 29, 2007

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2007D-0168 Draft Guidances for Industry Describing Product-Specific Bioequivalence Recommendations; Availability

Dear Sir or Madam,

On behalf of the Johnson & Johnson Pharmaceutical Research and Development, I am providing the following comments and recommendations with regard the Food and Drug Administration's (FDA) Draft Guidances for Industry on Bioequivalence Recommendations for Specific Products, as published for consultation and comments in the Federal Register dated May 31, 2007, Docket No. 2007D-0168.

The company recognizes the usefulness of these guidelines containing drug-specific recommendations as these will facilitate consistence in bioequivalence approaches and submitted data in support of ANDA approvals, in concurrence with the regulatory expectations for innovator new drug products.

The Company wishes to submit several recommendations to enhance and optimize the guideline, based on its extensive experience with products that were discovered, developed and commercialized by the Company.

General Comments

1. As discussed in the general FDA guidance[1] a bioequivalence (BE) study is intended to compare the systemic exposure profile of a test drug *product* to that of a reference drug *product* as a surrogate to demonstrate therapeutic equivalence. For two orally administered drug products to be bioequivalent, the active drug ingredient or active moiety in the test product must exhibit the same rate and extent of *absorption* as the reference drug product.

Turnhoutseweg 30, 2340 Beerse, Belgium - RPR Turnhout 4203 - VAT: BE-0403.834.160
Tel.: +32(0)14.60.21.11 - Telefax: +32(0)14.60.28.41 - E-mail: info@janbe.jnj.com - Cables: JANSSENPHARMA - Post Account: 000-0003331-33

Both from a physiological and from a statistical point of view, it is unlikely to observe drug product-specific gender differences in drug absorption rate or extent with the proposed study designs. Consequently, demonstration of bioequivalence in a male population is predictive for a female population.
Moreover, the inclusion of female volunteers in BE studies will increase the complexity of the study design, e.g. the need to synchronize the administration of the drug products to the periodicity of the female menstrual cycle.
Also, at the stage of ANDA's, extensive information on the disposition of the drug in female subjects is generally available. Consequently, BE studies, in particular for ANDA's, should not be intended to re-assess the pharmacokinetic characteristics of the active pharmaceutical ingredient for the proposed subgroups of the population such as female subjects.
Unnecessary increase in heterogeneity of the study population, not supporting the primary purpose and objective of BE studies, results in an increased variability in pharmacokinetic measures and, consequently, may confound the primary study objective to determine differences between two drug products.

In the absence of a clear scientific rationale to include female healthy volunteers in a BE study in support of its primary purpose and objectives, exposing female volunteers to any safety risk (or the fetus in case of undetected pregnancy) could be problematic or even unacceptable for some drug products.
We recognize that inclusion of female healthy volunteers in BE studies is preferred for drug products which are primarily or exclusively intended to be used in female populations. For the majority of drug products, however, including female subjects in BE studies will not result in additional relevant information on the use or dosing of the proposed drug product in female patients.

Therefore, we recommend the guideline to include statements, accepting justified requests to waive the recommendation to include female volunteers, for example if insufficient safety information is available to expose female volunteers to the drug or if otherwise inclusion of female subjects may compromise the primary objective of the BE study.

2. Since food-effect is an intrinsic characteristic of the drug *product*, a recommendation to submit a BE study under fed conditions, in addition to a BE study under fasted conditions, is generally appropriate for all drug products, unless i) sufficient information on the food effect of the reference and/or proposed drug product is available and submitted, and ii) the physicochemical characteristics (e.g. pH-dependency of solubility, permeability) provide sufficient justification that bioequivalence under fed conditions can be inferred from data obtained in a fasted BE study.

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3. In each of the product-specific recommendations, reference is made to the dissolution test methods, mostly in a single low-pH dissolution medium. In order to ensure interchangeability between different drug products in all patients, independent of the gastric pH, we recommend that – in addition to the dissolution release test at a single pH – comparative dissolution would normally have to be demonstrated over the full physiological gastric pH range (pH 1 to 6.8), especially i) for drugs with pH-dependent solubility, or ii) if no fed BE study is conducted, or iii) for drug products with a narrow therapeutic window.

4. The draft guideline does not include recommendations for galantamine IR tablets. We recommend to include separate recommendations for galantamine IR tablets, in line with the proposed recommendations for galantamine ER capsules.

Specific Comments on Product Specific Recommendations

Section	Comments
Risperidone tablet	The FDA proposes to conduct fasted and fed BE studies at a 1-mg strength, conditionally accepting waivers for lower and higher strengths. This would result in inference on bioequivalence at a fourfold higher dose strength, which is not necessary and not without risks. Since the rate and extent of dissolution of a drug product are concentration-dependent, differences in rate and extent of dissolution, and therefore of exposure between two drug products, are usually most prominent after administration of the highest strength. Therefore, demonstration of bioequivalence at the highest strength is generally considered the most sensitive approach to detect the absence of bioequivalence of different drug products. Demonstrating bioequivalence at the lower 1-mg strength is thus not necessarily predictive for the higher strengths. We therefore recommend including a recommendation to conduct a single-dose BE study in either schizophrenic patients stabilized on another antipsychotic at the highest strength (4 mg), or in healthy subjects with 2-mg strength. Both approaches have repeatedly and successfully been done in the past, without prohibitive tolerability issues. We concur that demonstration of bioequivalence based on the measurement of unchanged risperidone alone is sufficient and the most sensitive approach to qualify the proposed drug product.
Galantamine HBr ER capsule	There seems to be a discrepancy in the Dissolution method information between page 2 of the guidance document, which mentions using pH 6.8 buffer, and the link to the Dissolution Methods Database for Galantamine Hydrobromide ER capsules, which indicates 50 mM potassium dihydrogen phosphate buffer pH 6.5. We recommend to clarify this.

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	FDA recommends conducting BE studies at the lowest strength (8 mg) only. This would result in inference on bioequivalence at a three-fold higher dose strength (24 mg), which is not necessary and not without risks. Since the rate and extent of dissolution of a drug product are concentration-dependent, differences in rate and extent of dissolution, and therefore of exposure between two drug products, are usually most prominent after administration of the highest strength. Therefore, demonstration of bioequivalence at the highest strength is generally considered the most sensitive approach to detect the absence of bioequivalence of different drug products. Demonstrating bioequivalence at the lowest 8-mg strength is thus not necessarily predictive for the higher strengths. We therefore recommend including a recommendation to conduct a multiple-dose study with the 24-mg strength after an appropriate uptitration phase. This approach has repeatedly and successfully been done in the past, without prohibitive tolerability issues.
Itraconazole capsule	Demonstration of bioequivalence based on measurement of unchanged itraconazole alone is sufficient and the most sensitive approach to qualify the proposed drug product. However, FDA recommends measuring hydroxyitraconazole, an active metabolite of itraconazole, although no acceptance criteria are defined. We request FDA to justify its recommendation, and to consider limiting its recommendation to measurement of unchanged itraconazole only. We concur with the necessity to require a fed BE study because of the pH dependent solubility and the fact that food-effect is an intrinsic characteristic of the drug product that led to the label requirement of administering the drug under fed conditions. Conducting a fasted BE study in addition to a fed BE study is considered of limited scientific or clinical relevance, and waiving a fasted BE study should be feasible.
Flavoxate HCl Tablet	As detailed in the general comments (2nd comment) above, we recommend adding a recommendation to conduct a fed BE study if dissolution at high pH is not comparable with the reference drug product because of the pH-dependent solubility and because the food-effect is a characteristic of the drug *product*.
Topiramate Tablet	The FDA proposes to conduct fasted and fed BE studies at the 25-mg strength, conditionally accepting waivers for higher strengths. This would result in inference on bioequivalence at an eightfold higher dose strength, which is not necessary and not without risks. Since the rate and extent of dissolution of a drug product are concentration-dependent, differences in rate and extent of dissolution and therefore of exposure between two drug products are usually most prominent after administration of the highest strength. Therefore, demonstration of bioequivalence at the highest strength is generally considered the most sensitive approach to detect the absence of bioequivalence of different drug products. Demonstrating bioequivalence at the lower 25-mg strength is thus not necessarily predictive for the higher strengths. Additionally, because of the high affinity but low capacity binding of topiramate to carbonic anhydrase in red blood cells, single dose proportionality has not been

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	demonstrated at doses as low as 25 mg, and extrapolation of BE results from this low-strength tablet to higher strength tablets is therefore not appropriate. We recommend conducting BE studies in the patient population at the highest strength (200 mg) or in healthy volunteers with a 100 mg tablet. Because of the slow elimination of topiramate at low concentrations from its red blood cell binding sites (4 day half-life in whole blood), we recommend stipulating a 3-week washout between study periods.
Topiramate Sprinkle capsule	See above comment on washout period for topiramate tablets.

The Company concurs with the product-specific recommendations for Tramadol Hydrochloride tablets, Tramadol Hydrochloride/Acetaminophen tablets, and Almotriptan Maleate tablets.

In closing, we would like to thank the Agency in advance for its thoughtful consideration of our comments and recommendations.

Sincerely,

Paul A. Soons, PhD
Vice President, Clinical Pharmacology Worldwide
Johnson & Johnson Pharmaceutical Research & Development
a Division of Janssen Pharmaceutica N.V.

[1] Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations. Guidance for Industry. Food and Drug Administration, March 2003.

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