



American Society of Transplant Surgeons

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September 24, 2007

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

**Re: Docket Number 2007D-0168  
Draft Guidances for Industry Describing Product-Specific  
Bioequivalence Recommendations**

Dear Mr. Nguyen:

The American Society of Transplant Surgeons (ASTS) appreciates this opportunity to comment on the recently issued guidance from the FDA regarding bioequivalency testing requirements for development of generic immunosuppressive drugs. The ASTS is an organization comprised of over 1100 transplant surgeons, physicians and scientists dedicated to excellence in transplantation surgery through education and research with respect to all aspects of organ donation and transplantation so as to save lives and enhance the quality of life of patients with end stage organ failure. Our members, along with our medical colleagues, write or supervise the writing of essentially all prescriptions for the medications that enable successful transplantation. In addition, we are responsible for the monitoring of the safety and efficacy of these drugs and frequently must deal with their side effects and/or the consequences of non-compliance in our patients. For these reasons we are acutely interested in the testing methods utilized that bring all new drugs to our area of the pharmaceutical market.

2007A-0168

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**National Office**  
2461 South Clark Street  
Suite 640  
Arlington, VA 22202  
Phone: 703 414-7870  
Fax: 703 414-7874  
Email: [asts@asts.org](mailto:asts@asts.org)  
[www.asts.org](http://www.asts.org)

**President**  
Goran B. Klintmalm, MD, PhD  
Baylor Regional Transplant Inst.  
3500 Gaston Avenue  
Dallas, TX 75246  
Phone: 214 820-2050  
Fax: 214 820-4527  
Email: [gorank@baylorhealth.edu](mailto:gorank@baylorhealth.edu)

**President-Elect**  
John P. Roberts, MD  
Univ. of California San Francisco  
Division of Transplantation  
505 Parnassus Ave  
Box 0780, Room M896  
San Francisco, CA 94143-0780  
Phone: 415 353-1888  
Fax: 415 353-8709  
Email: [robertsj@surgery.ucsf.edu](mailto:robertsj@surgery.ucsf.edu)

**Secretary**  
Robert M. Merion, MD  
University of Michigan  
315 West Huron, Suite 240  
Ann Arbor, MI 48103-4262  
Phone: 734 936-7336  
Fax: 734 998-6620  
Email: [merionb@umich.edu](mailto:merionb@umich.edu)

**Treasurer**  
Michael M. Abecassis, MD, MBA  
Northwestern University  
Division of Transplantation  
675 N. St. Clair Street, #17-200  
Chicago, IL 60611  
Phone: 312 695-0359  
Fax: 312 695-9194  
Email: [mabecass@nmh.org](mailto:mabecass@nmh.org)

**Immediate Past President**  
Arthur J. Matas, MD

**Past President**  
A. Benedict Cosimi, MD

**Councilors-at-Large**  
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Kim M. Olthoff, MD  
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Alan N. Langnas, DO  
Richard B. Freeman, Jr., MD  
Dixon B. Kaufman, MD, PhD

**Executive Director**  
Katrina Crist, MBA  
Email: [katrina.crist@asts.org](mailto:katrina.crist@asts.org)

We recognize that the high cost of these medications can represent financial hardship for some of our patients and therefore we strongly support the introduction of lower cost generic alternatives. However, it is essential that before a generic product is introduced in the market place it undergo rigorous testing for bioequivalence in the very population of patients and under similar circumstances these products are designed to treat. We feel strongly that the currently proposed guidelines for demonstrating bioequivalence for transplant indications are far too loose and could be potentially dangerous. Transplant recipients almost always must be maintained on a variety of immunosuppressant and antibiotic medications which all have multiple potential interactions with each other. In addition, many other commonly prescribed medications (antihypertensives, cholesterol lowering agents, anti-fungals, antihyperglycemics) and many food types (citrus juices, fatty meals) can dramatically affect the metabolism of these drugs. Many transplant recipients have impaired organ function that also can affect the therapeutic window and toxicity of these medications. The proposed guidelines only require demonstration of bioequivalence in healthy subjects who may, or may not, be maintained on controlled diets, who by definition almost certainly will not be taking these other drugs, and who will not have organ dysfunction.

In addition, there is no mention in the guidelines about drug level monitoring and the correlation of single blood level measurements with overall drug exposure. Transplant clinicians and their patients rely heavily on the thoroughly documented relationships between these two indices for the existing compounds to ensure that patients receive adequate but not excessive exposure to these powerful drugs. Failure to provide these data for newly approved generic equivalents will put clinicians "in the dark" regarding proper dosing and will potentially expose patients to too much or too little drug. This problem is already widely recognized with the generic cyclosporine products where one generic can be substituted for another without physician input. When discovered, these switches require much more intensive blood level monitoring than would otherwise be required as the drug level on one generic drug dose are not the same as on another generic. This results in increased cost and hardship for patients. When not discovered in time, these variations in bioequivalence will result in graft dysfunction and loss. Our members have directly experienced such cases and we point out that in one multicenter trial with generic cyclosporine at one institution all patients on the generic experienced rejection.

Therefore, for our patients' safety and for their therapeutic benefit, we must emphatically suggest that bioequivalence studies for generic immunosuppressants must include stable transplant patients at the very least, and that they should be organ-specific. Establishing that a generic immunosuppressant is bioequivalent to the proprietary product in stable renal transplant recipients does not necessarily prove bioequivalence in liver or heart patients. The therapeutic window for these drugs varies by organ type and is too narrow in each to generalize for all. The consequences of being a little outside this window (either over or under exposed) are catastrophic for our patients.

We strongly urge the FDA to reconsider these guidelines for demonstration of bioequivalence for the immunosuppressant generics for the safety and efficacy of these medications in our patients.

Sincerely,

A handwritten signature in black ink, appearing to read "G. Klintmalm". The signature is fluid and cursive, with a large initial "G" and a long, sweeping underline.

Goran B. Klintmalm, MD, PhD, FACS  
President