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July 14, 2009

**BY HAND DELIVERY**

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
Department of Health and Human Services  
5630 Fishers Lane, Room 1061  
Rockville, Maryland 20852

Re: Bioequivalence Requirements for Modified Release Guaifenesin

**CITIZEN PETITION**

Reckitt Benckiser Group plc ("Reckitt") submits this Citizen Petition under section 505(b) and 505(j) of the Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act"),<sup>1</sup> to request that the Director of the Office of Generic Drugs ("OGD") of the Food and Drug Administration ("FDA") require that any Abbreviated New Drug Application (ANDA) referencing Mucinex®, Maximum Strength Mucinex®, Mucinex® D, or Mucinex® DM ("Mucinex® Products") modified-release ("MR") guaifenesin meet the same bioequivalence requirements required of Adams Respiratory Therapeutics, Inc. ("Adams"), previously a wholly-owned subsidiary of Reckitt and Reckitt's predecessor in interest, for approval of the referenced products, including demonstrating an early C<sub>max</sub> and efficacious concentrations throughout the 12-hour dosing interval.

**I. Actions Requested**

Reckitt submits that establishing bioequivalence in MR guaifenesin requires demonstrating a profile that is equivalent to the Mucinex® Products, namely a profile having an early C<sub>max</sub> that is equivalent to an immediate release product and a therapeutically effective concentration for the full 12-hour dosing interval. Reckitt respectfully requests that FDA take steps to ensure the bioequivalence and thus the effectiveness of any generic MR guaifenesin drug

<sup>1</sup> 21 U.S.C. §§ 355(b) and (j); 21 C.F.R. § 10.30

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products by requiring ANDA sponsors demonstrate the proposed product has that profile as well as measuring  $C_{\max}$  and AUC. To ensure that generic products have the same PK profile as the Mucinex® Products, and thus are not misbranded, generic products referencing the Mucinex® Products should be required to have an early  $C_{\max}$  and provide effective plasma concentrations for 12 hours.

## II. Brief Statement of Grounds

In a recent citizen petition, FDA was asked to consider whether “FDA [should] require that all ANDA applicants referencing Doryx DR Tablets conduct bioequivalence studies under all dosing conditions in labeling . . .” FDA answered affirmatively stating that “ANDA applicants must demonstrate bioequivalence under the dosing conditions described in the labeling.”<sup>2</sup>

In explaining the basis of that decision, FDA stated that bioequivalence measures include  $C_{\max}$  and AUC, and “[i]n addition, FDA carefully reviews the  $T_{\max}$  parameter of test and reference means, which is a measure of time to maximum plasma concentration [ . . . ]” The need to review  $T_{\max}$  was based presumably on FDA’s desire to ensure that the generic product had a comparable PK profile to that of the reference listed drug. As discussed below, FDA carefully reviewed the PK profile of Mucinex, and thus Reckitt submits that for ANDA products referencing the Mucinex® Products, FDA should likewise carefully examine the PK profile of the generic product, including  $T_{\max}$  and whether the generic product is therapeutically effective for 12 hours.

In the late 1990s, instead of joining the existing group of manufacturers that were marketing unapproved guaifenesin products purported to provide extended therapeutic effect, Adams elected to engage in a four-year process to obtain NDA approval for its MR guaifenesin product. As FDA had already determined that immediate release (“IR”) guaifenesin was safe and effective through its monograph review process, Adams based its NDA on showing bioequivalence to the monograph product.

Developing an MR product that FDA accepted as bioequivalent to the monograph involved considerable development work. Adams’ initial tablet was able to control the release of guaifenesin over a 12-hour period. However, while the  $T_{\max}$  for that initial tablet was about the same as an initial dose of an IR product, the magnitude of  $C_{\max}$  was not comparable to that of the IR product. FDA sent Adams a letter on May 4, 1999 noting that simulated steady state profiles showed that the MR product had a lower  $C_{\max}$  than the IR reference and required Adams either to demonstrate that this difference was inconsequential or to reformulate its tablets. Adams then reformulated its tablets.

The reformulated tablet consisted of an IR and SR layer. It provided the early  $C_{\max}$  boost (like an IR product) necessary for efficacy soon after dosing, and also provided a

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<sup>2</sup> Letter from Janet Woodcock, Acting Director Center for Drug Evaluation and Research, FDA, to Michael Halstead, Associate General Counsel Warner Chilcott, FDA Doc. No. FDA-2008-P-0586 (May 1, 2009), *available at* [www.regulations.gov](http://www.regulations.gov).

sustained release form of guaifenesin. In the 99-04 IND study, Adams demonstrated that its reformulated tablets were equivalent in  $C_{max}$  and AUC to the IR product. Under conventional standards for demonstrating bioequivalence, Adams had demonstrated bioequivalence at this point, because it had demonstrated equivalent  $C_{max}$  and AUC. However, FDA also looked carefully at the question of whether Adams' reformulated product was appropriate to dose at 12-hour intervals, as opposed to 8-hour intervals. FDA's concerns about the efficacy throughout the dosing interval were most clearly articulated in discussions about the 99-05 protocol (Adams' pivotal multiple-dose study) throughout the fall of 1999. Adams reformulated its drug product to address FDA's concerns and Mucinex was approved for dosing once every 12 hours.

Any generic product that purports to be bioequivalent to the Mucinex® Products must have the same PK profile as the branded product, namely an early  $C_{max}$  and 12-hour efficacy; otherwise, the generic product is misbranded. As noted above, FDA has recently confirmed for other generic products that its review is not confined simply to  $C_{max}$  and AUC, but that FDA will consider other important PK parameters and characteristics of the product for which approval is sought. For example, in its recent May 1, 2009 response to the Doryx citizen's petition referenced above, FDA indicated that it carefully reviews  $T_{max}$  during its review of generic products. Adams' experience demonstrates the challenges involved in designing an MR guaifenesin product that achieves  $C_{max}$  in a timely manner while continuing to deliver an effective dose for twelve hours. Even when Adams had achieved equivalence in terms of AUC and  $C_{max}$ , FDA insisted on further evidence to demonstrate therapeutically effective concentrations in the last four hours of the dosing interval. To avoid the risk that a purported generic equivalent is misbranded as having a release profile like Mucinex, generic applicants should similarly be required to demonstrate that their generic product has an early  $C_{max}$ , and provides effective plasma concentrations to justify a 12 hour dosing interval.

### **III. Environmental Impact**

The actions requested in this petition are subject to categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31(g).

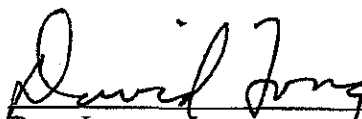
### **IV. Economic Impact**

Pursuant to 21 C.F.R. § 10.30(b), an economic impact statement will be submitted at the request of the Commissioner.

### **V. Certification**

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: November 6, 2006 (when Adams received a copy of FDA's bioequivalence recommendations for extended-release guaifenesin),

and May 1, 2009 (when FDA confirmed its review of ANDAs could extend beyond C<sub>max</sub> and AUC to include, for example, T<sub>max</sub> for ANDAs in its respect to Docket No. FDA-2008-P-0586). If I received or expect to receive payments, including cash and any other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: I am an employee and officer of Reckitt and am making these representations on behalf of Reckitt as part of my responsibilities as an employee and officer of Reckitt and am not being separately compensated for submitting this petition. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.



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