



Date: 1/12/10

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To: File 125325 / 10

Through: Dorothy Scott, M.D.; CBER/OBRR/DH/LPD; HFM-345; 301-827-3016

Cc: Cherie Ward-Peralta; OBRR/DBA/RPMB; HFM-380; 301-827-9170

Subject: Immunogenicity Assay Development

Product: Alpha-1 Proteinase Inhibitor (Human) intravenous for chronic augmentation and maintenance therapy in individuals A1PI deficiency and emphysema

Submission Date: December 28, 2009

Manufacturer: Kamada, Ltd.

The following letter-ready comments may be faxed to the Sponsor:

1) Use of a -----(b)(4)-----  
-----, is a good choice as a positive control. However your calculation of sensitivity for  
the positive control assumes all of the antibody in the positive control is directed against  
A1PI. This is invalid, -----(b)(4)-----  
-----, and only a small proportion of Ig in that preparation is A1PI directed.  
You can improve this by using an affinity purified antibody preparation, in which  
essentially all of the Ig in the vial should bind A1PI.

2) From the description, it appears that the test samples are -----(b)(4)-----  
-----  
----- . Is this reading correct? It is a very reasonable approach to free



----- (b)(4) -----  
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Reviewer's comments:

1) Use of a commercially available A1PI directed antibody, ----- (b)(4) -----  
-----, is a good choice as a positive control. However your calculation of sensitivity for  
the positive control assumes all of the antibody in the positive control is directed against  
A1PI. This is invalid, ----- (b)(4) -----  
-----, and only a small proportion of Ig in that preparation is A1PI directed.  
You can improve this by using an affinity purified antibody preparation, in which  
essentially all of the Ig in the vial should bind A1PI.

2) From the description, it appears that the test samples are ----- (b)(4) -----  
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----- Is this reading correct? It is a very reasonable approach to free  
complexes with - (b)(4) -, but the freed antibody should be captured on A1PI - (b)(4) -  
----- is added. Based on the information you have provided, it may be  
feasible to capture A1PI directed antibodies from your --- (b)(4) --- samples, using A1PI  
beads. This approach might allow you to wash out free A1PI, nonspecific Ig, and other  
components of the sample which contribute to interference in your - (b)(4) - assay. Anti-  
A1PI antibodies can then be eluted from A1PI beads and quantitated with better accuracy  
than you are currently achieving (see comment 3).

3) In this assay it appears that serial dilutions of purified human IgG are ----- (b)(4) -----  
----- to provide the basis of an improvised standard curve. What is the efficiency of  
immobilization of your human IgG standard curve? If unknown, the assignment of  
antibody concentration based on the standard curve is not valid, and the assignment of  
sensitivity values based on the standard curve is also invalid.