



Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Biologics Evaluation and Research

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**Date:** 6/8/10

**To:** To File (STN 125325)

**From:** Ewa Marszal, PhD; CBER/OBRR/DH/LPD, HFM-345, 301-402-4368

**Through:** Dorothy Scott, MD; CBER/OBRR/DH/LPD, HFM-345, 301-827-3016

**CC:** Cherie Ward-Peralta, RPM; CBER/OBRR/DBA/RPMB, HFM-380, 301-827-9170

**Applicant:** Kamada

**Product:** Alpha-1-Proteinase Inhibitor (Human)  
Proposed name: GLASSIA

**Subject:** Visible particulates in the final container

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**Recommendation:** IR and PMCs. Please see the Letter-Ready Comments at the end of this memo.

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#### Presence of visible particles in licensed A1PI products

To establish whether visible particulates are present in all A1PI products, we requested samples submitted for release from the PRB. Our request was denied by the management for reasons of current policy with a suggestion that we may ask the A1PI manufacturers to voluntarily submit product samples for this purpose. This attempt was not continued because we did not wish to let manufacturers know that their products are not tested by CBER and that to be able to test, we need manufacturers' concurrence.

### Aralast

The PI states: “When reconstitution procedure is strictly followed, a few small visible particulates may occasionally remain. These will be removed by the microaggragate filter.” The filter (20 µm) is supplied with the product and is used for product pooling into an IV container. No in-line filter use during product administration is recommended.

### Prolastin-C

The PI states: “A few small particles may occasionally remain after reconstitution. If particles are visible, remove by passage through a sterile filter (e.g., 15 µm filter) used for administering blood products (not supplied).” A sterile filter needle with a pore size of approximately 150 (!) µm, which is supplied with the product, is used during product pooling into an IV container. No in-line filter use during product administration is recommended. I note that particles become visible at the size of ~50 µm and can be missed by an inexperienced eye. Thus, procedures for Prolastin-C are limited with respect to protection from injection of visible particulates.

### Zemaira

The PI states: “Parenteral drug preparations should be inspected visually for particulate matter and discoloration prior to administration.” Product filtration in-line during administration through a 5 µm filter (not supplied) is recommended.

### Kamada-API

The product contains protein particles (details discussed below). Kamada-API is filtered through a 5 µm filter needle supplied with the product during pooling into an IV container and will be filtered again through a 5 µm filter (not supplied) recommended for in-line filtration during product administration. Thus, Kamada recommends the best filtration conditions of the product just prior to administration compared to other API products.

### Examples of other protein products containing protein particulates

#### Remicade® (Centocor)

(for IV injection)

The following language is in the PI: “Allow the reconstituted solution to stand for 5 minutes. The solution should be colorless to light yellow and opalescent, and the solution may develop a few translucent particles as infliximab is a protein. Do not use if opaque particles, discoloration, or other foreign particles are present.” and “The infusion solution must be administered over a period of not less than 2 hours and must use an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2 µm or less).”

#### Enbrel® (Immunex)

(for subcutaneous injection)

The following language is in the PI: “Prior to administration, visually inspect the solution for particulate matter and discoloration. There may be small white particles of protein in the solution. This is not unusual for proteinaceous solutions. The solution

should not be used if discolored or cloudy, or if foreign particulate matter is present.” and “Do not filter reconstituted solution during preparation or administration.”

Stelara™ (Cilag AG)

(for subcutaneous injection)

The following language is in the PI: “Prior to administration, Stelara™ should be visually inspected for particulate matter and discoloration. Stelara™ is colorless to light yellow and may contain a few small translucent or white particles. Stelara™ should not be used if it is discolored or cloudy, or if other particulate matter is present.” I did not notice any recommendation regarding filtration of the product before or during injection.

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### **LETTER-READY COMMENTS**

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Please agree to the following post-marketing commitments and please provide wording for these commitments in a Letter of Post-Marketing Commitments:

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Twenty (20) Pages Determined to be Non-Releasable: (b)(4)