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January 20, 2004

HAND DELIVER

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

Re: Comments of Madaus AG on Laxative Drug Products for Over-the-Counter Human Use: Reopening of the Administrative Record, Docket No: 78N-036L

Dear Sir or Madam:

On behalf of Madaus AG and in accordance with FDA's October 22, 2003 reopening of the administrative record, we submit the enclosed comments regarding the tentative final monograph for over-the-counter laxatives.

Sincerely,



Michelle L. Butler

MLB/map

Enclosures

78N-036L

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**Comment to  
Laxative Drug Products for Over-the-Counter Human Use  
Federal Register 50,2124-2158(1985)**

**Section §334.18 "Stimulant laxative active ingredients"**

The Tentative Final Monograph [Fed. Register Vol. 50, 2124-2158 (1985)] defines under Section §334.18h:

"Sennosides A and B from any of the following sources: senna leaf powder, senna fluid extract, senna fruit extract, senna syrup, senna pod concentrate, or sennosides A and B crystalline."

It is proposed to change this definition as follows:

"Senna leaf or senna fruit from *Cassia senna L.* (*Cassia acutifolia Delile*) or *Cassia angustifolia Vahl* as powder, or extract or an isolated mixture of hydroxyanthracene glycosides calculated as sennoside B".

According to the WHO Monograph, Vol. 1 (enclosure 1), the ESCOP Monograph (2<sup>nd</sup> edition, enclosure 2) or the Ph.Eur. Monograph (enclosure 3) senna leaf or senna fruit contain hydroxyanthracene glycosides (calculated as sennoside B), of which the most important are sennoside A and B.

The senna extracts in the market are more or less highly enriched with respect to the sennosides but there is no "sennosides A and B crystalline" available in the market. The only patented isolated mixture of hydroxyanthracene glycosides (which is not marketed) contains ca. 43% sennoside A and ca. 37 % sennoside B with <3% sennoside A1, C,D, or D1 and an overall purity of about 90%. (US patent 4,595,592 dated Jun. 17, 1986; Grimminger et al., enclosure 4).

Isolated hydroxyanthracene glycosides with a lower content of sennosides should be better categorized as extracts of senna leaf or senna fruit.

The basic analytical method for the hydroxyanthracene derivatives of senna is a spectrophotometric method which sums up not only the sennosides A and B but all the hydroxyanthracene derivatives (i.e. sennosides A, A1, B, C, D, D1; sennidin monoglucosides A, B; sennidins A, B; rhein glucoside; aloe-emodin glucoside; rhein; aloe-emodin; emodin) which contribute all to the clinical efficacy (Grimminger et al., enclosure 4).

The dosage given in section § 334.60 [subsection (d) "Directions", subsection 12 and 13] of the Tentative Final Monograph is for instance 12 to 50 mg once or twice daily for adults and children over 12 years of age. It is assumed that this dosage recommendation is based on the spectrophotometric method (calculated as sennoside B) as this method was the standard analytical method at that time and today (see Ph. Eur. Monograph). And it should be kept in mind that all the dosages reported in clinical studies worldwide with senna or preparations thereof have been based on this spectrophotometric method.

In this respect, this analytic method should be considered in the Final Monograph.

If the dosage recommendation of the Tentative Final Monograph will be based on a HPLC method and only sennosides A and B are measured or even if this HPLC method is done for the sennosides A, B, C and D this will result in an overdosing of senna plant drug (as powder or extract) of about 20-30 % compared to an analysis according to the spectrophotometric method.

**Paragraph 334.30 (Permitted combinations of active laxative ingredients)**

Paragraph 334.30, section (c) should be amended with the following combination in a new

subsection (3) :

"Plantago ovata husks identified in §334.10 (f)(1) and senna leaf or fruit identified in §334.18 (h)" [see above]

and with the following combination in a new subsection (4) :

"Plantago seed identified in §334.10 (f)(2) and senna leaf or fruit identified in §334.18 (h)" [see above]

Furthermore paragraph 334.30 (Permitted combinations of active laxative ingredients), section (a) should be amended with the following combination in a new subsection (4) :

"Plantago seed identified in §334.10 (f)(2) and Plantago ovata husks identified in §334.10 (f)(1)".

These amendments are necessary to allow OTC drug laxative products which are a combination of Senna, Plantago seed and Plantago ovata husks and which are marketed as safe and effective OTC drug products in the US market and worldwide.

Madaus AG  
Cologne, 15. January 2004

i.V. Dr. Georg Seidel