



The Purdue Frederick Company

One Stamford Forum
Stamford, CT 06901-3431
(203) 588 5000
Fax (203) 588 8850
www.purduepharma.com

April 12, 2004

5712 04 APR 13 11:5

SUBMITTED IN QUADRUPLICATE

Division of Dockets Management
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

RE: Citizen Petition: OTC Docket No. 1978N-036L

Dear Sir or Madam:

The Purdue Frederick Company ("Purdue") herewith submits this Citizen Petition under 21 CFR §10.30 requesting the Commissioner of Food and Drugs to re-open the administrative record associated with the OTC Tentative Final Monograph for Laxative Drug Products as proposed under Subpart B of 21 CFR Part § 334 to allow for submission and evaluation of additional comments. Alternatively, should this petition not be granted, we ask FDA to include our submission as a comment into the final administrative record.

Action Requested

Purdue requests the following actions:

- 1) A reopening of the OTC Laxative Monograph docket for the purpose of receiving the attached reply comment, which was not provided for in the original reopening of the docket; and
- 2) Rejection of the comments submitted by Hyman, Phelps & McNamara on behalf of Madaus AG (Cologne, Germany).

Statement of Grounds

A comment to the reopened docket contains material statements which Purdue knows to be inaccurate, and which are believed to be potentially damaging to a number of OTC product manufacturers. Purdue refutes the data and request in the Madaus comments (Attachment 1) based on the current information presented below.

Background

On October 22, 2003, the Food and Drug Administration (FDA) announced a reopening of the administrative record for "Laxative Drug Products for Over-the-Counter Human Use." On January 20, 2003, Hyman, Phelps & McNamara submitted comments on behalf of Madaus AG. The Madaus comments regarding section 334.18 suggest that the US monograph be changed to reflect the European Pharmacopeia Monograph (Ph. Eur. Monograph). This suggested revision would require changing the definition of sennosides, the methodology of calculating the amount of sennosides, and changing the analytical methodology to reflect the Ph. Eur.

1978N-036L

Dedicated to Physician and Patient

CP29

Monograph. These changes, if implemented, will have a significant negative impact on the quantitation, production, and labeling of current senna products in the US.

For example, in the USP-27/NF-22 two varieties of senna are described: Alexandria Senna (*Cassia acutifolia* Delile), and Tinnevelly Senna (*Cassia angustifolia* Vahl). The USP 27 describes sennosides as:

“Sennosides is a partially purified natural complex of anthraquinone glucosides found in senna, isolated from *Cassia angustifolia* or *C. acutifolia* as calcium salts.”

The USP 27 also provides monographs for different products forms, including Senna, Senna Fluidextract, Senna Oral Solution, Senna Syrup, Sennosides, and Sennosides Tablets. Additionally, the USP 27 provides a certified reference standard (USP Sennosides RS) which is a mixture comprised primarily of Sennoside A and Sennoside B, and small quantities of other sennosides. The analytical assay method for sennosides in the USP 27 is a fluorescence assay method, that converts the sennosides to a fluorescence species which is measured in a fluorometer. The method responds strongly to Sennoside A, B,C, and D.¹ and achieves specificity to anthrone/anthraquinone based compounds, by the inherent selectivity that is characteristic of fluorescence spectroscopy. This method has been used in the United States for a number of years, and as a result, most senna formulations are based on analytical data resulting from this method.

The changes to the definition and analytical methods as proposed by Madaus AG would unnecessarily require the majority of senna manufacturers to revise, their formulations and test methods.

In contrast to the USP 27, the Ph. Eur. Monograph describes four different varieties of senna, Senna Leaf, Senna Leaf Dry Extract, Standardized, Senna Pods, Alexandrian (*Sennae fructus acutifoliae*), and Senna Pods, Tinnevelly (*Sennae fructus angustifoliae*). Sennosides are not described as such, but instead as “hydroxyanthracene glycosides, calculated as sennoside B (C₄₂H₃₈O₂₀; Mr 863)” Each of the monographs has a section for assay. There are two different assay procedures for the four varieties of senna, one for Senna Tinnevelly, Senna Leaf, and Senna Alexandrian, and a second method for Senna leaf dry extract, standardized. Both methods are wet chemical methods that rely on liquid-liquid extractions to isolate the anthrone/anthraquinone compounds, which are then hydrolyzed, and oxidized to form a red solution that is measured in a visible spectrometer. There is no reference standard described in the Ph. Eur. Monograph; all assays are based on a reported specific absorbance of sennoside B. There is also no test method for finished product.

Lastly, Purdue disagrees with the following Madaus AG statement and conclusion:

“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.”

Lane, A.C., Spectrofluorometric method for the determination of Hydroxylated Anthracene Derivatives and its application to the Assay of Senna Derivatives in Biological Tissues, Analytical Chemistry, Vol 45, no 11, 1973

Discussion

Purdue strongly recommends that the definitions and test methods put forth in USP-27/NF-22 be used as the model for the final OTC laxative drug monograph, not the Ph. Eur. Monograph. Our rationale for this recommendation are two fold.

First, the majority of US senna products are formulated based on the definitions, and test methods described in the current USP, since the Ph. Eur. Monograph is not the standard analytical method in the U.S. today. Changing the definition, or test methodology of sennosides, will require that the majority of senna manufacturers revise their formulation, test methods, and documentation. This will create a huge burden to US senna manufacturers, with no compensating gain in safety or efficacy.

Second, the test methodology described in the Ph. Eur. Monograph is inferior when compared to the test methods described in the current USP. For your convenience, we have highlighted a few of the deficiencies noted in the Ph. Eur. Spectrophotometric method(s):

1. No standard is run in the method, a specific absorbance is used instead. It is critical that a standard is run for each assay, to check for instrument performance, and to demonstrate that the system follows Beers law. It is not possible to conduct a system suitability procedure without a standard.
2. The method is a wet chemical extraction method, which is very complex, composed of multiple extractions, and reflux steps. This methodology is much more complex, and presents many more opportunities for error, when compared to the USP fluorescence method.
3. The extraction scheme is flawed, in that it does not utilize back extractions to ensure quantitative extractions. When a Liquid/Liquid extraction is utilized for quantitative measurements it is critical to use back extractions. When two phases are separated in a liquid/liquid extraction, some of the water layer is carried over in the organic layer, along with compounds that are water soluble. In order to correct for this, when an organic (chloroform) layer is isolated from an aqueous layer, if quantitative results are required, the chloroform layer should be re-extracted with fresh aqueous solvent, and the resultant aqueous layer added to the original aqueous layer to ensure that no analyte is lost when the chloroform layer is discarded. Additionally the extraction scheme for Senna Pods Alexandrian, Senna Pods, Tinnevelly, and Senna Leaf calls for an initial 15-minute reflux step in water. This condition (boiling water) has been shown to cause up to a 10% degradation of sennosides, which will lead to an absolute error of 10%. Finally, solutions are not brought up to a known volume following extractions, which can lead to significant analytical errors. The wet chemical methodology is much more dangerous than the USP method. Highly volatile/flammable solutions (ether) are used, as well as known carcinogens (chloroform).
4. Reporting the results as sennoside B is misleading, this assumes that all compounds will have a response equivalent to B. We know that each of the sennosides will break down to form different compounds under the reaction conditions of this method (some will form 2 moles of rhein, others will form one mole of aloe emodin and one mole of rhein, and others will form only one mole of rhein). It is these compounds (rhein and aloe emodin) that we are measuring, since they turn red under basic pH conditions. Each of the different

sennosides will have a different response, since each breaks down into different compounds, in different molar amounts, and each of the product compound will have a different molar absorptivity. Hence, the Ph. Eur. Monograph is inaccurate and will result in analytical errors.

5. The calculations in the Ph. Eur. Monograph are not clear. The units in the calculation for "percentage of Hydroxyanthracene glycosides expressed as sennoside B", do not give a percentage, it gives a value with the units AU/g. There is a factor without unit in all calculations that is not referenced; it is not clear where this value is obtained. Additionally there is a statement: "i.e. taking the specific absorbance of sennoside B to be 240". It is unclear how this value should be used, since it is not in the calculation for the "percentage hydroxyanthracene glycosides". It can be used to calculate the percentage of hydroxyanthracene glycosides using Beers law ($A=abc$) with the assumption that a 1cm path length is utilized. When this is done the value is close to the calculation of "percentage Hydroxyanthracene glycosides", but not exactly the same. This would suggest that either the calculation for "percentage hydroxyanthracene glycosides" is incorrect, or the specific absorbance of sennoside B is in error.

Conclusion and Actions Requested

Purdue strongly recommend that the USP-27/NF-22 be followed as the basis for dictating the definition and quantitation of senna active ingredients for the final monograph on Laxative Drug Products for Over-the Counter Human Use. These requests are based on the fact that the majority of US senna products are formulated based on the definitions and test methods described in the USP-27/NF-22. Changing the definition, or test methodology of sennosides, to reflect those discussed in the Ph. Eur. Monograph, will require that the majority of senna manufacturers revise their formulation, test methods, and documentation. This will create a huge burden to US senna manufacturers, with no compensating gain in safety or efficacy. Additionally the spectrophotometric test methodology outlined in the Ph. Eur. Monograph is an inferior wet chemical method for the following reasons:

1. No reference standard is available.
2. Extraction method is more complex and error prone.
3. The extraction scheme is flawed, and will introduce errors through degradation of analyte and loss of analyte during extractions.
4. The wet chemical methodology is more dangerous, since it utilizes highly flammable reagents, as well as a known carcinogen (chloroform).
5. Reporting results as sennoside B is misleading and incorrect.
6. The calculations in the Ph. Eur. Monograph are not clear.

Adopting the Ph. Eur. Monograph testing methodology, instead of the simpler and more accurate USP methodology would have a negative impact on the quality of senna produced in the United States. This would be a step backward not forward.

Certification

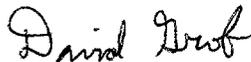
The undersigned certifies that, to the best of his/her knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data known to the petitioner to be unfavorable to the petition.

Concluding Remarks

The evidence provided above clearly illustrates the inaccuracy of the information presented in the comment submitted on behalf of Madaus AG. Purdue requests that FDA accept the comments and actions requested as presented in this Citizen for inclusion in the Final Monograph for Laxative Drug Products for Over-the-Counter Human Use.

Sincerely,

The Purdue Frederick Company
By:



David W. Grob, MS, RAC
Senior Director, Regulatory Affairs OTC
Purdue Pharma L.P.
Phone: (203) 588-8107
Fax: (203)588-6229

Enclosures

CC: Dr. Charles Ganley, FDA
Mr. Scott Bass, Esq., Sidley, Austin, Brown & Wood

Docket No. 1978N-036L
April 12, 2004

The Purdue Frederick Company

ATTACHMENT 1

LAW OFFICES

HYMAN, PHELPS & McNAMARA, P.C.

JAMES R. PHELPS
 PAUL M. HYMAN
 ROBERT A. DORMER
 STEPHEN H. McNAMARA
 ROGER C. THIES
 THOMAS SCARLETT
 JEFFREY N. GIBBS
 BRIAN J. DONATO
 FRANK J. SASINOWSKI
 DIANE B. McCOLL
 A. WES SIEGNER, JR.
 ALAN M. KIRSCHENBAUM
 DOUGLAS B. FARQUHAR
 JOHN A. GILBERT, JR.
 JOHN R. FLEDER
 MARC H. SHAPIRO
 FRANCES K. WU

700 THIRTEENTH STREET, N.W.
 SUITE 1200
 WASHINGTON, D. C. 20005-5929
 (202) 737-5600
 FACSIMILE
 (202) 737-9329
 www.hpm.com

MARY KATE WHALEN
 JENNIFER B. DAVIS
 OF COUNSEL

DAVID B. CLISSOLD
 CASSANDRA A. SOLTIS
 JOSEPHINE M. TORRENTE
 MICHELLE L. BUTLER
 ANNE MARIE MURPHY
 PAUL L. FERRARI
 JEFFREY N. WASSERSTEIN
 MICHAEL D. BERNSTEIN
 LARRY K. HOUCK
 DARAS KATCHER*
 KURT KARST
 MOLLY C. ANDRESEN*

*NOT ADMITTED IN D.C.

ROBERT T. ANGAROLA
 (1945-1996)

DIRECT DIAL (202) 737-7551

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

2603 MAIN STREET
 SUITE 760
 IRVINE CALIFORNIA 92614
 (949) 553-7400
 FAX (949) 555-7433

4819 EMPEROR BOULEVARD
 SUITE 400
 DURHAM, NORTH CAROLINA
 27703
 (919) 313-4750
 FAX (919) 313-4751

C 211

2004 JAN 20 11:22:29

**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 (2nd 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