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November 3, 2003

BY HAND DELIVERY

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

Re: Comments on Laxative Drug Products for Over-the-Counter Human Use: Proposed Amendment to the Tentative Final Monograph Docket No: 78N-036L

Dear Sir or Madam:

On behalf of Madaus AG (Madaus), the enclosed comments are submitted in response to the above-captioned proposed rule by the Food and Drug Administration (FDA) to amend the Tentative Final Monograph (TFM) for over-the-counter (OTC) laxatives to reclassify bulk-forming laxative psyllium ingredients in granular dosage form from Category I (generally recognized as safe and effective) to Category II (not generally recognized as safe and effective). Laxative Drug Products for Over-the-Counter Human Use: Proposed Amendment to the Tentative Final Monograph, 68 Fed. Reg. 46133 (Aug. 5, 2003) (Proposed Amendment).

Madaus manufactures the granular dosage laxatives Agiolax® (psyllium and senna) and Agiocur® (psyllium), previously distributed in the U.S. under the trade names Perdiem and Perdiem Fiber by (in turn) William H. Rorer, Inc. (Rorer), Rhone-Poulenc Rorer, and Novartis. These formulations are leading OTC laxative products in Europe and elsewhere in the world.

78N-036L

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Madaus disagrees with FDA's proposal to reclassify granular dosage forms of psyllium-containing laxatives. Madaus believes that neither the facts nor the law support such reclassification. Moreover, based on the record in this proceeding, it is clear that the inquiry by FDA was incomplete, confused, and biased, generating inaccurate results and unsubstantiated conclusions.

As discussed more fully in the attached comments, the risk-benefit record for the bulk laxative category as a whole demonstrates that these products are all safe and effective for their intended use. Bulk-forming laxatives in various forms, including granules, have provided safe and effective relief for consumers for some 50 years. The psyllium granular products are the preferred dosage form for millions of consumers worldwide.

In the Proposed Amendment, FDA is acting on information skewed to elicit adverse experience reports on granular products while failing to consider contemporaneous safety data on non-granular psyllium dosage forms. The agency ignores fatalities reported with non-granular psyllium products but emphasizes a single fatality associated with a granular form for which attribution is tenuous. FDA also fails to consider the benefits of granular psyllium products. See, e.g., J.A. Marlett, et al., Comparative Laxation of Psyllium with and without Senna in an Ambulatory Constipated Population, 80 Am. J. Gastroenterology, 333 (1987) (copy attached to Comments). In addition, FDA fails to take into account that stricter label warnings were required in 1993 for all products containing water-soluble gums.

Finally, the administrative record on which FDA relies in this proceeding is so flawed, biased, and inadequate that it raises significant questions of administrative due process. Cf. American Bioscience, Inc. v. Thompson, 243 F.3d 579 (D.C. Cir. 2001) (Court review must be based on the full administrative record); Hanover Potato Prods., Inc. v. Shalala, 989 F.2d 123 (3d Cir. 1993) (Attorneys fees awarded where FDA filed incomplete administrative record); United States v. Nova Scotia Food Prods. Corp., 568 F.2d 240 (2d Cir. 1977) (FDA improperly failed to disclose scientific research that was part of administrative record). The current record simply cannot support the Proposed Amendment.

If the agency were to go forward with this proposal, U.S. consumers would be deprived of safe and effective bulk laxative products, which are among the best selling laxatives worldwide. Madaus requests that FDA rescind or withdraw the proposal and retain Category I status for psyllium granular products.

Sincerely,

Paul M. Hyman
Counsel for Madaus AG

PMH/eam
Attachment
cc: Madaus AG

COMMENTS OF MADAUS AG ON LAXATIVE DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE: PROPOSED AMENDMENT TO THE TENTATIVE FINAL MONOGRAPH, DOCKET NO: 78N-036L

Madaus AG (Madaus) submits these comments in opposition to the Food and Drug Administration's (FDA's) above-captioned Proposed Amendment to the Tentative Final Monograph (TFM) for Over-the-Counter (OTC) Laxative Drug Products, which would reclassify granular psyllium dosage forms from Category I (generally recognized as safe and effective and not misbranded) to Category II (not generally recognized as safe and effective or misbranded). 68 Fed. Reg. 46133 (Aug. 5, 2003) (Proposed Amendment). As discussed in detail below, Madaus believes that granular psyllium dosage forms are safe and effective, as are all such bulk-forming laxative products, and that the record on which FDA relies to support the Proposed Amendment is incomplete, biased, confused, and inadequate.

I. Background

Madaus first introduced psyllium granules to the market in Europe in 1955. Based on tons sold, these products have been, and continue to be, the most widely used laxative drugs in the world. Perdiem and Perdiem Fiber were introduced into the U.S. market in 1980, although other psyllium-containing laxatives in granular dosage form may have been on the U.S. market before that time.

In 1985, FDA published a TFM for OTC laxatives that listed psyllium ingredients in Category I (generally recognized as safe and effective and not misbranded). 50 Fed. Reg. 2124 (Jan. 15, 1985). In the preamble to the TFM, FDA agreed with the opinion of the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products "that bulk-forming laxatives are among the safest of laxatives." Id. at 2131 (comment 33). FDA also noted that the Panel's recommendation for adequate fluid intake "was necessary for the proper use of bulk-forming laxatives because esophageal

obstruction has occurred when bulk-forming laxatives have been swallowed dry." Id. at 2132 (comment 37). Granular dosage forms were not singled out in that document.

In comments on the TFM, Rorer supported a stronger warning and a change in directions for use to provide that psyllium-containing laxatives be taken in divided doses, rather than as a single daily dose. Proposed Amendment, Reference 2.[1] The comments noted that "the overall incidence of esophageal obstruction appears to be quite low[,] . . . estimated at one case per one million to two million doses [of Perdiem] sold." Id. at 2. Rorer also took other steps, including sending a "dear doctor" letter and developing a patient package insert detailing proper use of the Perdiem products. Reference 4. In 1986, FDA adopted Rorer's suggestion and amended the TFM to propose divided doses rather than a single daily dose. 51 Fed. Reg. 35136 (Oct. 1, 1986).

In October 1989, FDA requested information from Rorer about esophageal obstruction associated with use of Perdiem products. Rorer reported 61 cases over the nine years following introduction of the product. Reference 1.[2] It is not clear what the incidence of similar adverse experiences might have been for other psyllium products during that period. However, in an August 6, 1990 letter responding to Rorer's comments on the 1985 TFM (more than 5 years later), FDA noted that "the agency has received other reports indicating that esophageal obstruction and asphyxiation have been associated with the ingestion of water-soluble gums, hydrophilic gums, and hydrophilic mucilloids, including psyllium." Reference 3 at 2. Thus, although Rorer reported 61 cases of esophageal obstruction, Madaus is not aware of a single incident of asphyxiation

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1 References cited hereinafter are those included in the Proposed Amendment. 68 Fed. Reg. at 46137.

2 These data were submitted by Rorer in a letter dated October 23, 1989, which was not included in the record. See Reference 4.

associated with granular forms of psyllium, and FDA has never notified the company of any such case.

Rorer responded to FDA on August 28, 1990, pointing out that only 15 of the 61 cases of esophageal obstruction had occurred after 1985, when the company had taken the actions cited above. Reference 4. That decrease occurred concomitantly with a 60% increase in unit sales during the period.

FDA then proposed a label warning for all OTC drug products containing water-soluble gums as active ingredients. 55 Fed. Reg. 45782 (Oct. 30, 1990). The warning applied to certain OTC weight loss products, which had been implicated in several fatalities, as well as to bulk-forming laxatives. The rule became final in 1993. 58 Fed. Reg. 45193 (Aug. 26, 1993); 21 C.F.R. § 201.319. The warning and directions alerted users of these products to consume adequate fluid and to avoid using such products if they had previously experienced any difficulty swallowing.

In issuing this final rule, FDA stated that the agency was aware of 191 cases of esophageal obstruction and 8 cases of asphyxia associated with OTC weight control and laxative products between 1970 and May 1992. (Of course, Perdiem was not on the market before 1980.) Eighteen deaths were reported, at least 13 of which involved asphyxiation and aspiration of powder products. None of the fatal cases involved granular forms of psyllium. Moreover, FDA did not single out granules in the 1993 final rule as raising any special risks.

The 1993 final rule and the warning it required mark the beginning of the most relevant time period for determining risk with these products. Since that date, as indicated in the Proposed Amendment, FDA has concentrated on psyllium products. Moreover, FDA eventually – and inexplicably – focused solely on granular dosage forms of psyllium, abandoning or ignoring serious adverse events associated with other forms of psyllium. FDA apparently used three mechanisms to attempt to capture the adverse

events related to psyllium products: FDA searched its AER database, conducted a review of the medical literature, and examined records it requested only from the U.S. distributor of Perdiem. 68 Fed. Reg. at 46135.

In November 2000, FDA reviewed AERs and literature on esophageal obstruction for psyllium products (Perdiem, Metamucil and Serutan) between 1966 and 2000. Reference 5. The agency identified 98 cases, of which 78 cases were reportedly related to the granular dosage form. Id. at 46134; Reference 6. The listing of these reported cases contains patient identification numbers but no product names. Reference 5. Sixty-one Perdiem cases had already been reported to FDA in 1989. Reference 1. The additional 17 case reports of esophageal obstruction from 1989 to 2000 (11 years) thus can hardly be considered a basis for increased safety concern. Despite acknowledging the existence of injuries and deaths from asphyxia associated with non-granular forms of psyllium, FDA chose to focus on the esophageal obstruction reportedly associated with granular psyllium products. Reference 6.[3]

FDA asserts that there were 4 deaths among the 98 reported cases, 3 associated with Metamucil and one with the granular dosage form. 68 Fed. Reg. at 46134. However, as the attached MedWatch report discloses, the death attributed to Perdiem in 1995 occurred 4 months after the patient was treated for the reported obstruction. Attachment 1. It seems quite unlikely that Perdiem caused that fatality.

In January 2001, FDA requested updated AERs only from Novartis for the Perdiem products. 68 Fed. Reg. at 46135. There is no indication from FDA that manufacturers of any other dosage forms were asked to provide similar information.

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[3] Although the Federal Register statement is inconsistent with the text of Reference 6, both point out that there were "13 . . . cases of choking-related events" associated with Metamucil, which included 2 cases of esophageal obstruction and 3 reported deaths. 68 Fed. Reg. at 46134; see Reference 6.

Novartis provided data from January 1999 through January 2001. Reference 7. The data were updated in April 2002. Reference 8. (Somehow, FDA reviewed AERs through May 2002. 68 Fed. Reg. at 46135.[4]) It is unclear whether the 1999 AERs, as well as some of the 2000 AERs, were counted in the November 2000 review, because Reference 6 does not list the AERs or patient identification numbers. More important, there is little information in the record pertaining to AERs for other psyllium-containing products during the same period, apart from the discussions in References 6 and 8/10.

Overall, there are confusing discrepancies among the more recent documents cited by FDA, no comprehensive list of AERs, and no coherent description of how FDA estimated the risks associated with Perdiem as compared to other psyllium products in the years following the 1993 warning.

Based on biased, incomplete, confused, and highly selective information, FDA has now proposed to find that granular forms of psyllium are not generally recognized as safe for OTC laxative use. Madaus disagrees with that proposal, disputes the agency's concerns over the safety of the dosage form, and differs with the agency's data gathering and evaluation techniques.

II. The Data Cited by FDA in Support of its Proposed Action Do Not Support Such Action

FDA has proposed to move granular psyllium products from Category I to Category II based on conclusions drawn from incomplete data that are inadequate to support such action. FDA believes that granular psyllium products present an

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[4] This is one of many examples of confusing discrepancies in the record. Even more confusing is the fact that References 8 and 10 are the same document, although they are listed with different titles and dates in the Federal Register. 68 Fed. Reg. at 46137. FDA has responded to repeated requests for clarification with assurances that the two references are, indeed, the same document.

"unacceptable health risk to consumers," basing this conclusion on reports of esophageal obstruction and choking associated with use of the products. 68 Fed. Reg. at 46135. FDA's conclusion is drawn from its review of AERs it has received, the medical literature, and other information submitted by a distributor of a granular psyllium product (Novartis) in response to a specific request by FDA for AER information. The data that FDA has analyzed, and upon which it relies for its conclusion that the granular psyllium products are not safe, support neither the conclusion nor the proposed action.

The overall safety analysis conducted by FDA in this proceeding is biased and cannot be considered a comprehensive review of the issue. Without articulating its reasons, FDA focused on the granular psyllium products, requesting information on adverse events from the U.S. distributor of Perdiem but not trying to obtain the necessary comparative information from manufacturers of psyllium powder or wafer products. In so doing, FDA ignored information suggesting that powder products presented similar or possibly more significant safety issues, particularly the risk of asphyxiation. Moreover, FDA's analysis of the safety data overstates the seriousness of the events related to the granular psyllium products and fails to take into account the fact that the number of events potentially related to granular psyllium products is very small in relation to the number of doses taken by consumers.

A. FDA's Analysis Concentrated Improperly on Granular Psyllium Products

FDA's analysis of the information regarding adverse events was not comprehensive and focused improperly on granular psyllium products, despite the fact that the same data contained information suggesting that the powder psyllium products may present more serious safety problems (e.g., asphyxiation). In its November 17, 2000 analysis of AERs from its database and review of the medical literature of esophageal obstruction and choking events related to psyllium laxative products, FDA found 3 deaths among 13 cases associated with use of a powder or wafer psyllium product. Reference 6.

In contrast, FDA found 1 death out of 78 cases associated with the granular psyllium product. Moreover, that one reported fatality was almost certainly not caused by the granular product, in light of the fact that, according to the AER, the patient died four months after her treatment for esophageal blockage. See Attachment 1.

Given the higher number of deaths (in absolute terms and in relation to the number of reported events) associated with use of powder psyllium products, FDA's conclusions concerning the risks of granules appear unsupportable. At the very least, these data should have led FDA to request records from the powder manufacturers, as it did with the leading distributor of the granular product. No credible, unbiased comparison of the safety of the various psyllium products can be made when data are available for only one of these products, especially when the 1993 warning applied to all such OTC drug products. Nevertheless, FDA turned its attention only to granular dosage forms.[5]

B. FDA's Analysis of the Data Overstates the Risks of Granular Psyllium Products

FDA's discussion of the data overstates the relative number of adverse events associated with granular psyllium products because the AERs consist mostly of listings by Rorer and Novartis specifically requested by FDA. No similar requests were made to marketers of powder or wafer products, with the result that FDA relied only on the sparse and sporadic AERs filed for such products. The failure to employ the same methods to obtain AERs for both granular and non-granular psyllium formulations undermines FDA's conclusion that only the granular form poses an unacceptable risk. There are no comparable data on powder or other psyllium dosage forms.

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[5] The risk of asphyxiation with powder psyllium products is real and continuing. See D.M. Hunsaker et al., Therapy-Related Café-Coronary Deaths: Two Case Reports of Rare Asphyxial Death In Patients Under Supervised Care, 23 Am. J. Forensic Med. & Pathology, 49 (2002) (Attachment 2).

FDA stated that it has received 142 reports of adverse events regarding esophageal obstruction and choking associated with psyllium between 1966 and May 2002. 68 Fed. Reg. at 46135.[6] FDA obtained 98 of these events by searching its AER database and the medical literature from 1966 to 2000. Reference 5. It included other dosage forms of psyllium products, as well as granules. The other 44 events, reported between 1999 and 2002, were received from only one granular psyllium distributor. References 8 and 9. Because the other manufacturers were not asked for AERs for the same time period and in the same manner, the comparison of the data for granular dosages versus other forms is invalid.[7]

From the FDA references and data presented, it is not possible to determine what terms were used to search for AERs. Reference 5 contains patient identification numbers, but no product names. Reference 6 contains no line-listing and no patient identification numbers. Reference 9 contains no patient identification numbers. These omissions make the analyses of the different lists and references very difficult to compare and likely to be inaccurate.[8]

III. FDA Failed to Consider the Benefits of Granular Psyllium Products

In concluding that granular psyllium products should be moved from Category I to Category II for safety reasons, FDA failed to consider the benefits of granular psyllium

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6 It would be interesting and relevant to examine comparative rates of esophageal obstruction and choking associated with ingestion of food.

7 Moreover, FDA's risk analysis inexplicably failed to address at least 13 deaths associated with non-granular psyllium products reported prior to 1993. See 58 Fed. Reg. at 45195-96 (Reference 1) (Aug. 26, 1993).

8 It is also odd to note that the analysis in Reference 10 compares Senna (Senokot granules) with psyllium products (Perdiem, Metamucil and Serutan). Senokot granules do not contain water-soluble gums and were not considered in the 1993 analysis. This comparison again seems biased.

products. While FDA has never suggested that granular products are not effective, the agency has ignored the fact that this form is preferred by millions of consumers over powders or other forms. FDA is obligated to consider the efficacy and benefits of these products, as well as the preference of consumers.

In that connection, at least one published clinical study suggests that granular psyllium products are more effective than the powder products. An adequate and well-controlled study conducted in constipated subjects in the U.S. in 1986, reported in a peer review journal, showed Perdiem (granular psyllium and senna) significantly superior to Metamucil (powder psyllium) with respect to efficacy as measured by stool frequency, moisture content, and weight. J.A. Marlett, et al., Comparative Laxation of Psyllium with and without Senna in an Ambulatory Constipated Population, 80 Am. J. Gastroenterology, 333 (1987) (copy attached as Attachment 3). The study illustrates the benefits of the granular product, as acknowledged by both FDA and the Advisory Review Panel by their placement of the product in Category I.

IV. FDA Should Consider Foreign Safety Data

Madaus understands that in 2001 Novartis provided FDA with European safety data on its granular psyllium products. In addition, Madaus is attaching to these comments documents that demonstrate that, since 1980, Madaus has received reports of 3 serious[9] and 5 non-serious[10] adverse events related to dysphagia and esophageal

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9 These serious events were recorded by Madaus as follows: 1 case of esophageal obstruction coded as dysphagia; 1 case of foreign body sensation coded as dysphagia; and 1 case of foreign body sensation coded as dysphagia plus vomiting.

10 These non-serious events were recorded by Madaus as follows: 1 case of nausea and vomiting and 4 cases of esophageal obstruction coded as dysphagia.

obstruction for Agiolax (Perdiem), and only 6 serious[11] and 2 non-serious[12] for Agiocur (Perdiem Fiber). Attachments 4 and 5. None of these events resulted in death or serious injury, and all patients recovered. Given that the Agiolax products are leading laxatives in these countries, the small number of serious adverse events reported demonstrates the safety of the products.

FDA's analysis of the safety of the granular form of psyllium should consider this information, which further demonstrates that the Proposed Amendment lacks scientific support.

V. Conclusion

Based on the foregoing, it is clear that the proposal to amend the TFM for laxatives to reclassify granular dosage forms of psyllium from Category I to Category II is based on flawed and inadequate data and analyses and is improper as a matter of fact and law. FDA should rescind or withdraw the Proposed Amendment and retain Category I status for granular psyllium products.

Respectfully submitted,

Martin Schata, M.D.
Member of the Board of Directors
Madaus AG
Cologne, Germany

Dated: November 3, 2003

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11 These serious events were recorded by Madaus as follows: 4 cases coded as dysphagia; 1 case of dysphagia and choking; and 1 case of dysphagia, choking, and vomiting.

12 These non-serious events were both recorded by Madaus as dysphagia.