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Division of Dockets Management (HFA-305)
Food and Drug Administration
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Re: Amending the Monograph for Over-The-Counter Laxative Drug Products to Include the Combination of Bisacodyl and Docusate Sodium; Comments on Docket No. 1978N-036L, 68 Fed. Reg. 60302, October 22, 2003.

Dear Sir or Madam:

On behalf of Boehringer Ingelheim Pharmaceuticals (“BI”), we are submitting comments in response to the reopening of the administrative record for the rulemaking involving the final monograph for Over-The-Counter (“OTC”) Laxative Drug Products. On October 22, 2003, the Food and Drug Administration (“FDA”) published a notice in the Federal Register (68 Fed. Reg. 60302) inviting public comment on certain matters in this record. In that notice, FDA indicated that good cause allowed for the inclusion of all new data and information that were submitted to the docket after the administrative record closed for various proposed amendments to the tentative final monograph (“TFM”) for OTC laxative drug products. The agency further indicated that, as provided under its regulations, it would hold the record open for an additional 90 days to allow interested parties to comment on this new information being included in the administrative record.

In these comments, BI responds to FDA’s conclusion in August 1995 that scientific data, as submitted to the agency at that time, do not establish the safety and efficacy of a combination product containing bisacodyl and docusate sodium (“DSS”). The agency reached that conclusion after the administrative record closed for the proposed amendment to the TFM involving docusate salts. 58 Fed. Reg. 46589 (Sept. 2, 1993). Specifically, just days before the deadline for comments were due on that proposal, CIBA Consumer Pharmaceuticals (“CIBA”) filed data with FDA supporting its request for an amendment to the monograph allowing for combination use of

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DSS with bisacodyl.¹ A year later, however, FDA rejected CIBA's request after finding that the "submitted studies do not meet acceptable standards for documenting the safety and efficacy of the bisacodyl/DSS combination for OTC laxative use."² As set forth in detail below, more recent data and developments strongly support a finding by the agency that a combination product containing bisacodyl and DSS would be safe and effective for this use.

A. The FDA Has Consistently Acknowledged the Need for Laxative Products That Combine a Stimulant Laxative and a Stool Softener

At the outset, BI wishes to emphasize that FDA has long recognized the importance of allowing manufacturers to market a product that combines a stimulant laxative with a stool softener. Indeed, when FDA first proposed to establish a monograph for OTC Laxative products in 1975, its Advisory Review Panel stated "that combining two active ingredients may in some circumstances be desirable. For example, in an individual whose bowel movements are both painful and infrequent, a product combining a stimulant laxative with a stool softener may be rational."³ To address this need, and on the basis of recommendations from the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Anti-Emetic Products, FDA proposed to establish four combinations of a stimulant laxative with the stool softener, DSS, as safe and effective products. These stimulant laxatives were: danthron, casanthranol, phenolphthalein, and senna concentrate.⁴

¹ See Letter from Vincent De Stefano, Manager, Regulatory Affairs, CIBA Consumer Pharmaceuticals, to Dockets Management Branch (HFA-305), Food and Drug Administration, August 30, 1994. (Exhibit A). CIBA submitted these comments because bisacodyl was not included in the list of allowable stimulant laxative combinations with DSS (stimulants listed were casanthranol, phenolphthalein, and sennosides A and B). Although CIBA's letter as written was dated August 30, 1984, it was date-stamped October 6, 1994, and (according to FDA) was not filed as a comment in the docket until July 5, 1995.

² See Letter from William E. Gilbertson, Director, Monograph Review Staff, Office of OTC Drug Evaluation, to Vincent De Stefano, Manager, Regulatory Affairs, CIBA Consumer Pharmaceuticals, August 3, 1995. (Exhibit B)

³ See "Proposal to Establish Monographs for OTC Laxative, Antidiarrheal, Emetic, and Anti-Emetic Products," 40 Fed. Reg. 12902, 12921 (March 21, 1975).

⁴ The Panel considered only those combination products for which information had been submitted in response to a Federal Register notice of February 8, 1973 (38 Fed. Reg. 3614). The panel indicated that other combination products may be in the marketplace but that it did not have sufficient information to make a reasonable judgment about safety. However, it indicated that additional combinations could be approved through review and amendment of the monograph. See 40 Fed. Reg. at 12921

In connection with its review of these stimulant laxatives over the years, FDA has determined that three of these possible combinations could not be generally recognized as safe and effective. The agency concluded that danthron and phenolphthalein had significant carcinogenic potential, and, thus, were not safe and effective. 64 Fed. Reg. 4535 (Jan. 29, 1999). In addition, FDA decided that casanthranol should be assigned to Category III status because no data had been submitted concerning its carcinogenic potential. 67 Fed. Reg. 31125 (May 9, 2002). At the same time, FDA has found that other stimulant ingredients, including cascara sagrada and aloe, could also not be accorded category I status since there was insufficient information concerning their carcinogenic potential. *See* 67 Fed. Reg. 31125 (May 9, 2002).

Thus, of the four possible combinations of stimulant laxatives and stool softeners proposed by FDA in its initial OTC monograph more than 25 years ago, only one combination – DSS and senna – remains and has reached the market. Moreover, the field of possible stimulant laxatives to combine with DSS has narrowed substantially. In fact, only two stimulant laxative ingredients are now being considered for inclusion in the final monograph – senna and bisacodyl. As a result, in the decade that has passed since FDA rejected CIBA’s request for a bisacodyl/DSS combination product, the general situation involving approval of such products has changed dramatically. And, it is in this more recent context that bisacodyl must be considered for inclusion in a combination product with DSS.

B. A Combination Product Involving Bisacodyl and Docusate Satisfies Each of the FDA’s Requirements Governing Approval of Such Products

At the same time that various studies have ruled out certain stimulant laxatives, pre-clinical and clinical data collected by BI during the past ten years make clear that a bisacodyl/DSS product satisfies FDA’s requirements governing approval of combination products. In pertinent part, FDA’s regulations provide that an OTC drug that combines two active ingredients may be generally recognized as safe and effective if: (1) each active ingredient in the combination product is determined to be safe and effective; (2) each active ingredient makes a contribution to the claimed effect(s) of the product; (3) the combination of such ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and (4) when used under adequate directions for use and warnings against unsafe use, the combination product provides “rational concurrent therapy” for a significant proportion of the target population.⁵ 21 C.F.R. § 330.10(a)(4)(iv).

⁵ FDA’s decisions on combination products are also governed by the agency’s guidelines for such products. Those guidelines were issued in September 1978, subsequently published in the Federal Register (*See* 43 Fed. Reg. 55466 (Nov. 28, 1978)), and posted on FDA’s website as a guidance document. These guidelines provide that Category I active ingredients from the same therapeutic category but with different mechanisms of action may be combined if the combination meets the OTC

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Turning to the first of these requirements, BI notes that FDA has completed its review of bisacodyl and determined it to be safe and effective. The FDA reached that conclusion after exhaustive studies evaluating the carcinogenic potential of bisacodyl.⁶ And, on the basis of those studies and other information available to the agency, the Division of OTC Drug Products has advised BI that the data support the safety of bisacodyl as a Category I OTC laxative ingredient.⁷ In that letter, the Division further advised BI that it intends to include an amendment to the final monograph that codifies this conclusion. Accordingly, in contrast to the situation involving bisacodyl in 1994, FDA has now reviewed studies and affirmatively determined that this active ingredient should be generally recognized as safe and effective.

Moreover, with respect to the second regulatory requirement for OTC combination products, studies undertaken by BI since 1994 demonstrate that bisacodyl is a highly effective stimulant laxative. For example, in one of these studies, bisacodyl was shown to have significant advantages in efficacy with respect to frequency of bowel movements and stool consistency in comparison to a placebo.⁸ This was a placebo controlled double blind study in constipated patients (28 bisacodyl, 27 placebo), who were treated for 3 days with bisacodyl. BI found that efficacy was better for bisacodyl compared to placebo in relieving constipation.

The third criterion governing approval of OTC combination products focuses on whether the combination decreases the safety or efficacy of either active ingredient. BI is not aware of any pharmacokinetic interactions between bisacodyl and DSS that would detract from the safety or efficacy of either ingredient. Moreover, FDA's previous finding that a phenolphthalein/DSS combination does not impact the safety or efficacy of either ingredient suggests that the same should be true of a bisacodyl/DSS product. That is because bisacodyl and phenolphthalein belong to the same structural and functional class of esteric compounds (biphenolmethane derivatives) and maintain similar pharmacological characteristics. The FDA previously

combination policy in all other respects and, "on a risk-benefit basis, the combination product is equal to or better than each of the active ingredients used alone at its therapeutic dose" (emphasis added).

⁶ Senna is still being reviewed for long term safety. BI understands that a final report on a two year oral carcinogenicity study supporting the safety of senna-containing OTC laxatives will be submitted to the agency by the end of March 2004.

⁷ See Letter from Charles Ganley, Director, Division of OTC Drug Products, to Dr. Martin Kaplan, Vice President, Drug Regulatory Affairs, Boehringer Ingelheim, Feb. 16, 2000 (Exhibit C).

⁸ See Vix, Krakauer, and Reed; Comparative Safety and Efficacy of Bisacodyl Sugar Coated Tablets in the Treatment of Constipation (U98-0150) (Exhibit D).

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recognized the chemical similarity of phenolphthalein and bisacodyl when it investigated the carcinogenic potential of these ingredients.⁹

Combined products containing bisacodyl and DSS have been approved for marketing in various foreign countries. For example, Dulcolax-S® (5 mg. bisacodyl and 16.75 mg. DSS) has been on the market in South Korea since 1989. Another combination of these two active ingredients, Dulcodos® (5 mg. bisacodyl and 8.5 mg. DSS), was approved in South Korea in 1988. The bisacodyl-DSS combination (5 mg. bisacodyl and 100 mg. DSS) was marketed under the brand name Dulcodos in Argentina, Canada, Ireland and the United Kingdom from 1967 to 1991. Another marketed version of the bisacodyl-DSS combination is Florisan® (5 mg. bisacodyl and 10 mg. DSS), which was registered in 1969 in Greece and is currently marketed as an OTC product there.

Finally, as to the remaining requirement, there can be no question that FDA has found that a combination product involving a stimulant laxative and a stool softener provides “rational concurrent therapy” for a significant proportion of the target population. As mentioned earlier, FDA’s Advisory Review Panel on OTC Laxative Products indicated in 1975 that a product combining a stimulant laxative with a stool softener may be rational. 40 Fed. Reg. 12902, 12921 (March 21, 1975). Although the particular types of active ingredients to include in such a product has been winnowed down as the TFM has undergone review, nothing has caused FDA to change its mind about the utility and importance of combining these types of active ingredients in one product. Hence, a combination of bisacodyl and DSS would also provide “rational concurrent therapy,” and thus satisfies the fourth requirement governing combination products.

C. The FDA Has Previously Approved Combination Products Without Requiring Additional Clinical Studies

In concluding that a bisacodyl/DSS combination product satisfies FDA’s regulatory requirements, BI is certainly mindful of FDA’s determination in 1994 that data, as then submitted by CIBA, did not support a finding of safety and efficacy for this product. It is important to emphasize, however, that FDA was not able to conduct a thorough evaluation of these studies before reaching that conclusion. That was because CIBA only submitted brief synopses of each study. Moreover, in response to a direct request from FDA for more detailed

⁹ Although FDA had found that initial tests evaluating the carcinogenic potential for bisacodyl were negative, it remained concerned about bisacodyl because of its chemical similarity to phenolphthalein. To address those concerns, FDA reopened the administrative record, proposed to reclassify bisacodyl from Category I to Category III status, and invited parties to undertake additional studies of bisacodyl to evaluate its carcinogenic potential. 63 Fed. Reg. 33592 (June 19, 1998).

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information, CIBA indicated that the original data for these studies could not be located and no additional information was available. The studies that CIBA relied on its submission were undertaken in 1964 and 1967. As a result, FDA based its earlier determination on a bisacodyl/DSS combination product on a review of brief and limited summaries of older clinical studies.¹⁰

In light of more recent information concerning the safety and efficacy of bisacodyl, BI respectfully urges FDA to revisit its earlier decision on this product and the agency's apparent conclusion that clinical studies are needed before this combination can be approved as safe and effective. Indeed, BI has identified at least three instances in which FDA has classified combinations of drug products as Category I (safe and effective) without requiring additional clinical data to support the effectiveness of such combinations. Specifically, FDA did not require additional data in support of the effectiveness of combinations in the monographs for OTC antacid (simethicone and an antacid), laxative (bulk and stimulant laxatives), and anorectal drug products (not requiring final formulation testing of combination products and accepting the combinations as formulated). *See* 68 Fed. Reg. 51167 at 51168 (Aug. 26, 2003).

In each of these cases, FDA focused on the safety and effectiveness of each active ingredient, the rationale for concurrent therapy, the contribution each ingredient makes to the combination, and the marketing history to support Category I classification of combinations. For example, FDA relied on an extensive record of marketing history for combinations of an antacid and simethicone, an antiflatulent, both of which are ingredients with different indications.¹¹

¹⁰ For this reason, it is not surprising that FDA was concerned that the studies provided no details concerning subject matching, randomization, inclusion/exclusion criteria, compliance, baseline laxation, dietary influences, and predefined statistical analyses, among others.

¹¹ FDA created an antiflatulent monograph in the tentative final order on antacid and antiflatulent products without publishing a call for the submittal of new data for a combination antiflatulent-antacid drug product comprising simethicone. Instead, the agency relied on the status of simethicone as a known antiflatulent and the historical use of simethicone-antacid combination products. *See* 38 Fed. Reg. 31260 (Nov. 12, 1973). Simethicone was marketed as a single ingredient antiflatulent at the time. FDA believed that while the antacid reduced the acid level in the stomach, the simethicone had a different pharmacological mode of action in which it reduced the surface tension of bubbles present in the stomach. In keeping with the principles of its rational combination policy, FDA approved a simethicone-antacid combination because it believed that such a combination would provide a rational therapy for a target population comprising those individuals who have acid indigestion, sour stomach, heartburn, and gas. *See Final Order for Antacid and Antiflatulent Products Generally Recognized as Safe and Effective and not Misbranded*. 39 Fed. Reg. 19862, 19871 (Jun. 4, 1974).

Furthermore, FDA also approved the combinations of bulk and stimulant laxatives in the laxative TFM (50 Fed. Reg. 2124, at 2152 and 2153 (Jan.15, 1985)) without requesting additional clinical data for approval. FDA's approval was based on the recommendations of the Advisory Review Panel for OTC Laxative Drug Products that reviewed such laxative combinations and recommended approval based on the requirement that each active ingredient had to make a contribution toward laxation.¹²

D. Approval of a Product Combining Bisacodyl and DSS Would Establish a Viable Alternative In This Therapeutic Class

Both senna and bisacodyl compete globally for the stimulant laxative market. Global sales of bisacodyl-containing OTC laxative products totaled over \$170 million in the fiscal year ending September 2003; in comparison, global sales of senna-containing OTC laxative products totaled over \$174 million. In the United States, retail sales of senna products declined by 9.7% in 2003 versus the prior year. Bisacodyl sales in 2003 exceeded 12.7 million packages and are now selling at a ratio of approximately 1:1 as compared to senna products. Thus, based on overall sales figures in the United States, American consumers view bisacodyl as a viable, even preferred, stimulant laxative product.

In light of FDA's expressed policy of promoting rational concurrent therapy involving stool softeners and stimulant laxatives, and consumer confidence in bisacodyl-containing products, a bisacodyl-DSS combination product would obviously be a logical alternative to the single stool softener/stimulant laxative combination product currently available in the United States. An alternative to the senna/DSS combination would provide therapy to those who cannot take senna products and those who prefer the efficacy of bisacodyl over senna. At the same time, the existence of such an alternative would promote consumer savings through price competition. In other therapeutic areas, alternative products have played an important role in maximizing consumer options.¹³ The same would be true here.

¹² In the advanced notice of proposed rulemaking for OTC laxative, antidiarrheal, emetic, and antiemetic drug products (40 Fed. Reg. 12902 at 12906 (Mar. 21, 1975)), the advisory review panel recommended Category I status for OTC bulk laxative psyllium ingredients. The panel also recommended a combination bulk laxative-stimulant laxative product based on the historically known concurrent use of both categories of laxatives by individuals. The FDA concurred with the panel recommendation and approved the inclusion of this combination in the tentative final monograph. No additional clinical data were submitted to FDA for this approval.

¹³ For example, pseudoephedrine became increasingly important when PPA was withdrawn from the market. Along the same lines, various cough/cold multi symptom combinations have optimized consumer options.

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Accordingly, the risks and benefits of a bisacodyl/DSS combination product are different today than in 1995, when FDA rejected CIBA's request for Category I status for this product. At the time of that decision, there were several stimulant/stool softener combination products available to the consumer. Today, only one possible alternative to a senna/DSS product exists – bisacodyl and DSS. And, bisacodyl has shown itself to be important to consumers. Therefore, FDA's response to CIBA of almost ten years should not prejudice or dispose of BI's request. Rather, since bisacodyl is better known now than it was ten years ago and is the only viable candidate for inclusion in an alternative combination product, FDA should recognize that the benefits of a bisacodyl-DSS combination outweigh any potential risks associated with this product.

E. Conclusion

Based on the foregoing and other data available to FDA, BI respectfully requests FDA to adopt an amendment to the final monograph for OTC Laxative Products to permit the combination of the stimulant laxative, bisacodyl, with the stool softener, DSS.

Thank you for your consideration of these comments.

Sincerely,

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Exhibits: as stated