



## **Time and Extent Application (TEA) Review for Sodium Picosulfate**

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**Office of Nonprescription Products**  
Center for Drug Evaluation and Research • Food and Drug Administration  
Rockville • MD 20857

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<b>CONDITION</b>	Sodium picosulfate, up to 10 mg
<b>PHARMACOLOGICAL CLASS</b>	Stimulant laxative
<b>MONOGRAPH</b>	OTC Laxative Drug Products (21 CFR part 334)
<b>APPLICANT</b>	Ropes & Gray, LLP 700 12 <sup>th</sup> Street, NW, Suite 900 Washington, DC 20005-3948 (202) 508-4600 on behalf of Boehringer Ingelheim
<b>SUBMISSION DATE</b>	June 24, 2005
<b>RECEIVED DATE</b>	June 27, 2005
<b>REVIEW DATE</b>	July 5, 2005
<b>REVIEWER</b>	Michael L. Koenig, Ph.D.
<b>TEAM LEADER</b>	Matthew R. Holman, Ph.D.

## BACKGROUND

The applicant requests addition of up to 10 mg sodium picosulfate, as a single active ingredient, to the monograph for OTC laxative drug products (21 CFR part 334). This TEA does not request any changes (*e.g.*, labeling or testing) to the laxative monograph other than addition of sodium picosulfate.

## REVIEWER'S COMMENTS

The applicant has provided basic information about sodium picosulfate, including a detailed chemical description as required in 21 CFR 330.14(c)(1)(i). Although sodium picosulfate is not included in the U.S. Pharmacopeia-National Formulary (USP-NF), the applicant notes that sodium picosulfate is recognized in two compendial standards:

- European Pharmacopoeia 5.0 (Exhibit B in the TEA)
- Japanese Pharmacopoeia XIV (Exhibit C in the TEA)

The applicant states that, if FDA finds sodium picosulfate eligible for further consideration in the monograph system, it will develop a proposed USP monograph for the compound.

Sodium picosulfate has been marketed as an ingredient in laxative products since 1966. Currently, laxative products containing sodium picosulfate are marketed in more than 60 countries on every continent except Antarctica (Table 1). Originally, in most countries, sodium picosulfate-containing laxative products were available only by prescription. Now, in nearly all of these countries, sodium picosulfate-containing laxative products are marketed directly to consumers (*i.e.*, without a prescription). In two countries (Japan and Pakistan), sodium picosulfate-containing laxative products are marketed simultaneously as non-prescription and prescription drug products. For commercial reasons, the sponsor (Boehringer Ingelheim, BI) has not requested a Rx-to-OTC switch in 11 countries: Chile, Costa Rica, the Dominican Republic, El Salvador, Greece, Guatemala, Honduras, Indonesia, Nicaragua, Panama, and Peru. Therefore in these countries, sodium picosulfate is currently available only by prescription. The applicant points out that requests for OTC status "have never been denied in any countries."

Sodium picosulfate-containing laxative products are not registered at all in Poland. The applicant states that BI had conducted toxicology studies “decades” prior to submitting an application for registration in Poland, and that Polish authorities required that more current studies be conducted. The applicant claims that the additional study requirements were “a matter of formality” and not due to any safety concerns. According to the applicant, the studies have not been conducted, because Poland represents a “very limited marketing opportunity.”

The applicant selected five countries to serve as the basis of this TEA: Brazil, Germany, Italy, Portugal, and the United Kingdom (UK). These countries are indicated in bold print in Table 1. Laxative products containing sodium picosulfate have been marketed directly to consumers in each of these countries for over 10 continuous years.

**TABLE 1. Countries where sodium picosulfate is marketed.<sup>1</sup>**

Europe (25)	Africa (12)	Asia/Pacific (15)	North/South America (15)
Austria	Djibouti	Australia	Argentina
Belarus	Egypt	Indonesia <sup>3</sup>	<b>Brazil</b>
Belgium	Ethiopia	Iraq	Chile <sup>3</sup>
Bulgaria	Eritrea	Japan <sup>2</sup>	Columbia
Czech Republic	Kenya	Jordan	Costa Rica <sup>3</sup>
Denmark	Libya	Kazakhstan	Dominican Republic <sup>3</sup>
Estonia	Malawi	Korea	Ecuador
Finland	Mauritius	Lebanon	El Salvador <sup>3</sup>
<b>Germany</b>	Somalia	Pakistan <sup>2</sup>	Guatemala <sup>3</sup>
Greece <sup>3</sup>	Sudan	Palestine	Honduras <sup>3</sup>
Hungary	Tanzania	Phillipines	Mexcio
<b>Italy</b>	Uganda	Taiwan	Nicaragua <sup>3</sup>
Latvia		Turkmenistan	Panama <sup>3</sup>
Lithuania		Uzbekistan	Peru <sup>3</sup>
Malta		Yemen	Venezuela
Moldova			
Netherlands			
Norway			
<b>Portugal</b>			
Slovakia			
Spain			
Switzerland			
Sweden			
Ukraine			
<b>United Kingdom</b>			

<sup>1</sup> Selected countries shown in bold print

<sup>2</sup> Available in prescription and non-prescription forms

<sup>3</sup> Available only by prescription

As indicated in § 330.14(b)(2), extent of marketing is determined by the extent to which sales meets the requirements outlined in § 330.14(c)(2)(ii), (c)(2)(iii), and (c)(2)(iv). These paragraphs collectively address the adequacy of the markets and marketing to reveal “infrequent but serious ADEs” (adverse drug events) that may occur in the U.S. population if FDA finds the condition generally recognized as safe and effective (67 FR 3060 at 3065).

Section 330.14 (c)(2)(ii) specifies that the applicant provide the “cumulative total number of dosage units sold for each dosage form of the condition.” In this case, the applicant reported the number of all packages of product sold in the five countries. The applicant reported the number of dosage units by two methods:

- (1) calculation based on the largest package size of each formulation sold worldwide (Table on page 7 of the TEA)
- (2) the actual number of each package size for each formulation sold in each of the five selected countries (Table on pages 8-14 of the TEA)

Based on the first method, the applicant estimates that 73.9 million dosage units have been sold worldwide since 1987. Based on the second method, the total number of dosage units sold in the selected countries is 76.7 million. Because the number of dosage units for the selected countries exceeds the number sold worldwide, it appears to this reviewer that the worldwide figure greatly underestimates the actual number of dosage units sold worldwide.

Section 330.14 (c)(2)(iii) requires a description of population demographics “to ensure that the condition’s use(s) can be reasonably extrapolated to the U.S. population.” The applicant provides information about the population demographics in each of the countries in tabular form on pages 9-13 of the TEA and states that the demographics in these countries is similar to U.S. demographics. I believe that there is an under-representation of people of African descent in the five selected countries. However, I believe that the worldwide marketing, which includes 12 African countries (see Table 1), reflects the diversity of the U.S. population.

Section 330.14 (c)(2)(iv) requires an explanation of the “use pattern.” Use pattern is defined as how often the product is used (according to the label) and for how long. According to the

submitted labeling, laxative products are to be taken once a day in the evening with laxation occurring 10-12 hours later. Labeling advises consumers not to take laxative products for prolonged periods of time (*e.g.*, no more than 7 days for GUTTALAX liquid and capsules distributed in Italy) and to see a doctor if laxatives are needed every day. Labeling in the selected countries consistently directs adults to take 5 or 10 mg before bedtime. In contrast, labeled directions for children vary significantly between the selected countries (Table 2). With the exception of dosing directions for children, the indications, warnings, and directions included in the labeling are generally comparable to those outlined in proposed 21 CFR 334.60(b), (c), and (d), respectively (50 FR 2124 at 2155-2156, January 15, 1985). The applicant needs to explain the variation in children's dosing regimens, recommend a single, uniform children's dosage for this product in the United States, and explain how that dosage was determined.

**TABLE 2. Dosing regimens for children**

Brazil	Children 4 - 10 years old: 2.5 - 5.0 mg/day Children under 4 years: 0.25 mg/kg body weight/day
Germany	Children older than 4 years: 2.5 - 5.0 mg/day Children less than 4 years: DO NOT USE
Italy	Children 3 - 12 years old: See a doctor Drops: 0.13 - 2.0 mg/day Capsules: 2.5 mg/day (ages 4 - 10) Children less than 3 years: DO NOT USE
Portugal	Children: see a doctor Children 4 - 10 years old: 2.5 - 5.0 mg/day Children under 4 years: 0.25 mg/kg body weight/day
U.K.	Children greater than 10 years: 5 - 10 mg/day Children less than 10 years: See a doctor

The applicant does not indicate that any serious or unresolved ADEs have been reported for sodium picosulfate-containing laxative products. The regulatory agencies in the selected countries require manufacturers to report serious ADEs, as FDA requires in the United States. The applicant notes that four of the five selected countries are listed in section 802(b)(1)(A) of the Federal Food, Drug, and Cosmetic Act (the Act). Inclusion in section 802(b)(1)(A) of the

Act has been interpreted to indicate that the regulatory systems in these countries are of comparable sophistication to that in the United States (64 FR 71062 at 71068). As a further indication of safety, the applicant states that laxative products containing sodium picosulfate have not been withdrawn from the market in any of the countries in which they are marketed.

### **RECOMMENDATION**

I recommend that sodium picosulfate, up to 10 mg, be considered eligible for review under the OTC drug monograph system. To be considered eligible for review under the TEA process, a product must meet the criteria of marketing for a material time and to a material extent as set forth in § 330.14(b)(2) (§ 201(p) of the Act). Sodium picosulfate meets the material time standard. The applicant selected five countries to serve as the basis for this TEA, and laxative products containing sodium picosulfate have been marketed directly to consumers in these countries for at least 10 continuous years. Sodium picosulfate also meets the criteria for marketing to a material extent. Over 76 million dosage units have been sold in the five selected countries. Furthermore, I believe the global market (more than 60 countries on 6 continents) adequately reflects the demographics of the U.S. market, and that ADE reporting in the 5 selected countries is adequate to detect any infrequent but serious adverse events. Finally, laxative products containing sodium picosulfate have not been withdrawn from the market in any of the countries in which they have been sold.