

contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

IX. Request for Comments

This final monograph establishes labeling for OTC antidiarrheal drug products containing bismuth subsalicylate and kaolin. The warnings for products containing bismuth subsalicylate in § 335.50(c)(2) include: (1) The Reye's syndrome warning in § 201.314(h), (2) "Allergy alert: Contains salicylate. Do not take if you are [bullet] allergic to salicylates (including aspirin), [bullet] taking other salicylate products," (3) "Do not use if you have [bullet] an ulcer [bullet] a bleeding problem," (4) "Ask a doctor or pharmacist before use if you are taking any drug for [bullet] anticoagulation (thinning the blood) [bullet] diabetes [bullet] gout [bullet] arthritis," (5) "When using this product a temporary, but harmless, darkening of the stool and/or tongue may occur," and (6) "Stop use and ask a doctor if [bullet] symptoms get worse [bullet] ringing in the ears or loss of hearing occurs [bullet] diarrhea lasts more than 2 days".

These warnings for products containing kaolin in § 335.50(c)(3) include: (1) "Ask a doctor or pharmacist before use if you are taking any other drugs. Try to use at least 3 hours before or after taking any other drugs," and (2) "Stop use and ask a doctor if [bullet] symptoms get worse [bullet] diarrhea lasts more than 2 days".

In addition, products containing either ingredient must state: (1) "Do not use if you have [bullet] bloody or black stool," and (2) "Ask a doctor before use if you have [bullet] fever [bullet] mucus in the stool". The agency notes that fever and use for more than 2 days were included in the "Do not use" warning proposed in § 335.50(c) of the TFM (51 FR 16138 at 16149).

The indications in this final rule are similar to those discussed in the TFM, and the directions in this final rule are based on the studies discussed in this document. While interested persons may comment on any portions of the labeling in this final rule, the agency would like to receive specific comments primarily on the warnings labeling in § 335.50(c).

This final rule also includes labeling requirements for products that meet the criteria established in § 201.66(d)(10) (see § 335.50(e)). This reduced labeling results from the modified labeling format for OTC drug products in § 201.66(d)(10), which did not exist when the TFM was published. Interested persons may also comment on this labeling.

The agency is particularly interested in receiving comments on the specific labeling requirements discussed in this section of this document. Comments should be identified with the docket number found in brackets in the heading of this document. Three copies of all written comments are to be submitted. Individuals submitting written comments or anyone submitting electronic comments may submit one copy. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday. If the comments justify a change in labeling, the agency will propose to amend the final monograph accordingly at a later date.

X. References

The following references are on display in the Dockets Management Branch (see ADDRESSES) under Docket No. 78N-036D and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Comment No. C85.
2. Comment No. C92.
3. Comment No. SUP12.
4. Letter from W. E. Gilbertson, FDA, to A. R. Giaquinto, Schering-Plough Corp., coded LET20.
5. Study IB-101, Comment No. CP2.
6. Steffen Study, Protocol PB-103, Comments No. CP2 and SUP10.
7. DuPont Study, Protocol PB-114, Comments No. CP2 and SUP10.
8. Letter from W. E. Gilbertson, FDA, to P. Sinnott, The Procter and Gamble Co., coded LET26.
9. Comment No. SUP8.
10. Comment No. SUP13.
11. Comment No. LET23.
12. Comment No. LET24.
13. Comment No. PR3.
14. Comment No. SUP14.
15. Comment No. TR1, pp. 43-46.
16. Letter from W. E. Gilbertson, FDA, to P. Sinnott, The Procter and Gamble Co., coded LET27.
17. Comment No. C94.
18. Gryboski, J. D. et al., "Bismuth Subsalicylate in the Treatment of Chronic Diarrhea in Childhood," *American Journal of Gastroenterology*, 80:871, 1985.
19. Soriano-Brucker, H. et al., "Bismuth Subsalicylate in the Treatment of Acute Diarrhea in Children: A Clinical Study," *Pediatrics*, 87:18-27, 1991.
20. Figueroa, D. et al., "Bismuth Subsalicylate Reduces Volume and Duration of Watery Diarrhea in Young Peruvian

Children," *Thirty-First Interscience Conference on Antimicrobial Agents and Chemotherapy*, Chicago, IL, Prog. Abstr. 31:224 (Abstr. No. 754), 1991.

21. Letter from W. E. Gilbertson, FDA, to P. Sinnott, The Procter and Gamble Co., coded LET29.

22. Comment No. PR8.

23. Comment No. CP3.

24. Comment No. SUP11.

25. Comment No. PR4.

26. Comment No. LET25.

27. Comment No. C89.

28. OTC Vol. 090005.

29. Comment No. SUP09.

30. Letter from W. E. Gilbertson, FDA, to G. H. Ishler, The Upjohn Co., coded LET2.

31. Comment No. MM8.

32. *The United States Pharmacopeia Dispensing Information*, 20th ed., Vol. I, United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 1869-1870, 1999.

33. OTC Vol. 090133.

34. Comment No. SUP5.

35. Comment No. AMD2.

36. Comment No. SUP6.

37. De Sola Pool, N. et al., "A Comparison of Nonsystemic and Systemic Antidiarrheal Agents in the Treatment of Acute Nonspecific Diarrhea in Adults," *Today's Therapeutic Trends*, 52:31-38, 1987.

38. DuPont, H. L. et al., "A Randomized, Open-Label Comparison of Nonprescription Loperamide and Attapulgite in the Symptomatic Treatment of Acute Diarrhea," *The American Journal of Medicine*, 88 supp. 6A:20-23, 1990.

39. Food and Drug Administration, "Guidelines for the Clinical Evaluation of Antidiarrheal Drugs," September 1977, in OTC Vol. 09DFM.

40. Letter from W. E. Gilbertson, FDA, to R. W. Soller, Nonprescription Drug Manufacturers Association, coded LET34.

41. Letter from W. E. Gilbertson, FDA, to R. W. Soller, Nonprescription Drug Manufacturers Association, coded LET39.

42. Rutledge, M. L. et al., "Clinical Comparison of Calcium Polycarbophil and Kaolin-Pectin Suspensions in the Treatment of Acute Childhood Diarrhea," *Current Therapeutic Research*, 23:443-447, 1978.

43. Rutledge, M. L. et al., "Calcium Polycarbophil in Acute Childhood Diarrhea," *Clinical Pediatrics*, 2:61-63, 1963.

44. Grossman, A. J., R. C. Batterman, and P. Leifer, "Polyacrylic Resin: Effective Hydrophilic Colloid for the Treatment of Constipation," *Journal of the American Geriatric Society*, 5:187-192, 1957.

45. Roth, J. L. A., "Effects of Polycarbophil as Enteral Hydrosorbent in Diarrhea," *American Journal of Digestive Diseases*, 5:965-971, 1960.

46. Pimparker, B. D. et al., "Effect of Polycarbophil on Diarrhea and Constipation," *Gastroenterology*, 40:397-404, 1961.

List of Subjects

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.