

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 02N-0496]

DMB

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Certifier D. Hawkins

**Agency Information Collection Activities; Submission for OMB Review;  
Comment Request; Aluminum in Large and Small Volume Parenterals Used  
in Total Parenteral Nutrition**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

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**SUMMARY:** The Food and Drug Administration (FDA) is announcing that the proposed collection of information listed below has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995 (the PRA).

**DATES:** Fax written comments on the information collection provisions by *[insert date 30 days after date of publication in the Federal Register]*.

**ADDRESSES:** Fax written comments on the information collection provisions to the Office of Information and Regulatory Affairs, OMB, Attn: Stuart Shapiro, Desk Officer for FDA, FAX 202-395-6974, or electronically mail comments to [sshapiro@omb.eop.gov](mailto:sshapiro@omb.eop.gov).

**FOR FURTHER INFORMATION CONTACT:** Karen L. Nelson, Office of Information Resources Management (HFA-250), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-1482.

**SUPPLEMENTARY INFORMATION:** In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

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**Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition—21 CFR 201.323 (OMB Control Number 0910–0439)—Extension**

FDA is requesting OMB approval under the PRA (44 U.S.C. 3501—3520) for the labeling requirements for aluminum content in large volume parenterals (LVPs), small volume parenterals (SVPs), and pharmacy bulk packages (PBPs) used in total parenteral nutrition (TPN). As explained in the final rule on aluminum content labeling requirements published in the **Federal Register** of January 26, 2000 (65 FR 4103), aluminum content in parenteral drug products could result in a toxic accumulation of aluminum in the tissues of individuals receiving TPN therapy. Research indicates that neonates and patient populations with impaired kidney function may be at high risk of exposure to unsafe amounts of aluminum. Studies show that aluminum may accumulate in the bone, urine, and plasma of infants receiving TPN. Many drug products used routinely in parenteral therapy may contain levels of aluminum sufficiently high to cause clinical manifestations. Generally, when medication and nutrition are administered orally, the gastrointestinal tract acts as an efficient barrier to the absorption of aluminum, and relatively little ingested aluminum actually reaches body tissues. However, parenterally administered drug products containing aluminum bypass the protective mechanism of the gastrointestinal tract and aluminum circulates and is deposited in human tissues.

Aluminum toxicity is difficult to identify in infants because few reliable techniques are available to evaluate bone metabolism in premature infants. Techniques used to evaluate the effects of aluminum on bone in adults cannot be used in premature infants. Although aluminum toxicity is not commonly

detected clinically, it can be serious in selected patient populations, such as neonates, and may be more common than is recognized.

FDA amended its regulations to add labeling requirements for aluminum content in LVPs, SVPs, and PBPs used in TPN. FDA specified an upper limit of aluminum permitted in LVPs and required applicants to submit to FDA validated assay methods for determining aluminum content in parenteral drug products. The agency added these requirements because of evidence linking the use of parenteral drug products containing aluminum to morbidity and mortality among patients on TPN therapy, especially among premature neonates and patients with impaired kidney function.

The information collection reporting requirements resulting from this rulemaking are as follows:

21 CFR 201.323(b)—Requires that the package insert of all LVPs used in TPN therapy state that the drug product contains no more than 25 micrograms per liter ( $\mu\text{g}/\text{L}$ ). This information must be contained in the “Precautions” section of the labeling of all LVPs used in TPN therapy.

21 CFR 201.323(c)—Requires that the maximum level of aluminum present at expiry be stated on the immediate container label of all SVP drug products and PBPs used in the preparation of TPN solutions. The aluminum content must be stated as prescribed in the regulation. The immediate container label of all SVP drug products and PBPs that are lyophilized powders used in the preparation of TPN solutions must contain the statement prescribed in the regulation.

21 CFR 201.323(d)—Requires that the package insert for all LVPs, SVPs, and PBPs used in TPN contain a warning statement, prescribed in the regulation, intended for patients with impaired kidney function and for

neonates receiving TPN therapy. This information must be contained in the “Warnings” section of the labeling.

21 CFR 201.323(e)—Requires that applicants and manufacturers must use validated assay methods to determine the aluminum content in parenteral drug products. The assay methods must comply with current good manufacturing practice requirements. Applicants must submit to FDA both validation of the method used and release data for several batches. Manufacturers of parenteral drug products not subject to an approved application must make assay methodology available to FDA during inspections. Holders of pending applications must submit an amendment to the application.

Compliance with the information collection burdens under §201.323(b), (c), and (d) (21 CFR 201.323(b), (c), and (d)) consists of submitting application supplements to FDA containing the revised labeling for each product. Based on data concerning the number of applications for LVPs, SVPs, and PBP used in TPN received by the agency, FDA estimates that the labeling for approximately 200 products will be changed under §201.323(b), (c), and (d). FDA estimates that it will take approximately 14 hours to prepare and submit to FDA each labeling change. FDA estimates that approximately 65 respondents will each submit 1 validated assay method annually under §201.323(e). FDA estimates that it will take approximately 14 hours to prepare and submit to FDA each validated assay.

In the **Federal Register** of December 19, 2002 (67 FR 77792), the agency requested comments on the proposed collection of information. No comments were received.

The burdens can be charted as follows:

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN<sup>1</sup>

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
201 323(b),(c),(d)	200	1	200	14	2,800
201 323(e)	65	1	65	14	910
Total					3,710

<sup>1</sup> There are no capital costs or operating and maintenance costs associated with this collection of information.

Dated: 3-10-03  
March 10, 2003.

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William K. Hubbard,  
Associate Commissioner for Policy and Planning.

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