and (a)(1)(ii) of this AD in accordance with the service bulletin. Where there are differences between the requirements of this AD and the procedures specified in the service bulletin, the AD prevails.

(i) Either repair chafed pipe assemblies or replace chafed pipe assemblies with new or serviceable pipe assemblies. And

(ii) Modify the FIREX and the pneumatic sense pipe assembly clamp marriage.

(2) If no chafing is detected, prior to further flight, modify the FIREX and the pneumatic sense pipe assembly clamp marriage in accordance with the service bulletin.

(b) An alternative method of compliance or adjustment of the compliance time that provides an acceptable level of safety may be used if approved by the Manager, Los Angeles Aircraft Certification Office (ACO), FAA, Transport Airplane Directorate. Operators shall submit their requests through an appropriate FAA Principal Maintenance Inspector, who may add comments and then send it to the Manager, Los Angeles ACO.

Note 2: Information concerning the existence of approved alternative methods of compliance with this AD, if any, may be obtained from the Los Angeles ACO.

(c) Special flight permits may be issued in accordance with sections 21.197 and 21.199 of the Federal Aviation Regulations (14 CFR 21.197 and 21.199) to operate the airplane to a location where the requirements of this AD can be accomplished.

Issued in Renton, Washington, on December 29, 1997.

Darrell M. Pederson,

Acting Manager, Transport Airplane Directorate, Aircraft Certification Service.

[FR Doc. 98–124 Filed 1–2–98; 8:45 am]

BILLING CODE 4910–13–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. 90N–0056]

Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its regulations to add certain labeling requirements concerning aluminum in large volume parenterals (LVP's) and small volume parenterals (SVP's) used in total parenteral nutrition (TPN). FDA is also proposing to specify an upper limit of aluminum permitted in LVP's and to require applicants to develop and to submit to FDA for approval validated assay methods for determining aluminum content in parenteral drug products. The agency is proposing these requirements because of evidence linking the use of parenteral drug products containing aluminum to morbidity and mortality among patients on TPN therapy, especially premature infants and patients with impaired kidney function.

DATES: Submit written comments by April 6, 1998. Submit written comments on the information collection requirements by February 4, 1998.

ADDRESSES: Submit written comments on this proposed rule to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Submit written comments on the information collection requirements to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB), New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, ATTN: Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT: Leanne Cusumano, Center for Drug Evaluation and Research (HFD–7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–2041.

SUPPLEMENTARY INFORMATION:

I. Background

Aluminum in ionic form is naturally present in all plant and animal tissues and in natural bodies of water, although it has no known biological function. Human exposure to aluminum also occurs through aluminum-containing medications, aluminum cans and cooking utensils, drinking water, baking powder, and deodorants (Ref. 1). Aluminum is found in public water supplies treated with various clarifiers and in food and drink, including infant formulas (Refs. 2, 3, and 4).

Aluminum is commonly found in dye lakes (coloring agents) and sometimes found as an excipient in certain drug products. It is usually found in parenteral drugs as a contaminant in the protein source, calcium and phosphate salts, albumin, and heparin (Refs. 5 and 6). Aluminum also leaches from glass containers and closures during autoclaving and storage.

Changes in the processing and screening of raw materials may reduce aluminum contamination of drug products. Aluminum toxicity in adults has been reduced by replacing casein hydrolysate with crystalline amino acids in TPN solutions (Ref. 7). In addition, the use of deionized water in dialysis and the substitution of calcium for aluminum-containing oral phosphate binders have reduced dialysis osteomalacia and encephalopathy.

FDA has become increasingly concerned about the aluminum content in parenteral drug products, which 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 (Refs. 2, 5, 6, and 8 through 13). Studies show that aluminum may accumulate in the bone, urine, and plasma of infants receiving TPN (Refs. 5, 8, and 9). 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 (Refs. 1, 3, 14, and 15).

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. One study indicated that premature infants who received parenteral therapy had higher than normal plasma and urinary aluminum concentrations. The study also indicated that aluminum concentration in bone marrow was 10 times higher in infants who had received at least 3 weeks of parenteral therapy than in those who had received limited parenteral therapy: 20.16±13.4 milligrams (mg) versus 1.98±1.44 mg per kilogram (kg) of dry weight ($p < 0.0001$) (Ref. 2). Furthermore, there has been at least one credible report of measurable aluminum in the brain of a premature infant (Ref. 16).

Classic manifestations of aluminum intoxication in patients with impaired kidney function include fracturing osteomalacia, encephalopathy, and microcytic hypochromic anemia. Aluminum may prevent calcium absorption in premature infants receiving TPN therapy (Ref. 9). In addition, aluminum loading may be a

factor in the bone disease of very ill neonates with reduced kidney function who have received long-term parenteral therapy with aluminum-contaminated fluids (Ref. 2).

FDA has held several meetings to discuss the risks posed by aluminum in parenteral drug products. On March 3, 1986, the agency's Advisory Committee on Endocrinologic and Metabolic Drug Products met to discuss the problems posed by aluminum in parenteral drug products (Ref. 22). The committee recommended that parenteral drug products intended for repeated use or given in large volumes over a short period of time be tested for aluminum levels. The committee also recommended that the agency establish an aluminum-contamination limit. On November 6, 1986, the agency held a public workshop to discuss aluminum toxicity in clinical medicine, existing aluminum monitoring, clinical effects of aluminum loading, and methodology for quantitative aluminum determination in parenteral products (Ref. 23). On June 25 and 26, 1987, the Allergenic Products Advisory Committee of FDA's Center for Biologics Evaluation and Research met to discuss the safety of the aluminum component of alum-precipitated allergenic extracts (Ref. 24).

As a result of the comments received at these meetings and because of the overall concern about the risks posed by aluminum content in parenteral drug products, FDA published a notice of intent in the **Federal Register** of May 21, 1990 (55 FR 20799). The notice announced the regulatory options the agency is considering and requested comments and data on the following issues: (l) Safe and unsafe levels of aluminum in LVP's, SVP's, and pharmacy bulk packages; (2) assay methodology; (3) units of measurement; (4) which drug products should be included in any aluminum content disclosure requirement; (5) suggestions for any warning statement required on parenteral drug product labeling; and (6) information concerning the economic effects of these regulatory options. The comments received on the notice of intent are discussed in section III of this document.

II. Description of the Proposed Rule

FDA is proposing to: (1) Establish a maximum permissible level of aluminum in LVP's used in TPN therapy; (2) require that the maximum level of aluminum permitted in LVP's used in TPN therapy be stated on the package insert of all LVP's used in TPN therapy; (3) require that the maximum level of aluminum at expiry be stated on the immediate container label of SVP's and pharmacy bulk packages used in the preparation of TPN solutions; (4) require that the package insert of all LVP's and SVP's, including pharmacy bulk packages, contain a warning statement about aluminum toxicity in patients with impaired kidneys and neonates receiving TPN therapy; and (5) require that applicants and manufacturers develop validated assay methods for determining the aluminum content in parenteral drug products and that applicants submit the validated assay methods to FDA for approval.

Proposed § 201.323(a) would limit the aluminum content for all LVP's used in TPN therapy to 25 micrograms per liter (µg/L) for liquids. This requirement would apply to all LVP's used in TPN therapy, including, but not limited to, parenteral amino acid solutions, highly concentrated dextrose solutions, parenteral lipid emulsions, saline and electrolyte solutions, and sterile water for injection.[1]

Proposed § 201.323(b) would require that the package insert for all LVP's used in TPN therapy state that the drug product contains no more than 25 µg/L. This statement would be included in the ''Precautions'' section of the labeling.

For SVP's and pharmacy bulk packages used in the preparation of TPN solutions, proposed § 201.323(c) would require that the product's maximum level of aluminum at expiry be stated on the immediate container label of the SVP's and pharmacy bulk packages. FDA is proposing that the statement on the immediate container label read as follows: ''Contains no more than __ µg/L.'' For those SVP's and pharmacy bulk packages that are lyophilized powders used in the preparation of TPN solutions, the maximum level of aluminum at expiry must be printed on the immediate container label as follows: ''When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than __ µg/L.'' The maximum level of aluminum may be expressed as the highest of: (1) The highest level for the batches produced during the last 3 years; (2) the highest level for the latest five batches, or (3) the maximum historical level, but only until completion of production of the first five batches after the rule takes effect. The labeling requirement would apply to all SVP's used in the preparation of TPN solutions, including, but not limited to: Parenteral electrolyte solutions, such as calcium chloride, calcium gluceptate, calcium gluconate, magnesium sulfate, potassium acetate, potassium chloride, potassium phosphate, sodium acetate, sodium lactate, and sodium phosphate; multiple electrolyte additive solutions; parenteral multivitamin solutions; single-entity parenteral vitamin solutions, such as vitamin K injection, folic acid, cyanocobalamin, and thiamine; and trace mineral solutions, such as chromium, copper, iron, manganese, selenium, and zinc.

Proposed § 201.323(d) would require that the package insert for all LVP's and SVP's, including pharmacy bulk packages, contain a warning statement about aluminum toxicity in patients with impaired kidney function and in neonates receiving TPN therapy. The warning statement would be included in the warning section of the labeling and would contain the following language:

WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

FDA is also concerned about the daily amount of aluminum received by patients with impaired kidney function. One study found that patients should not receive more than 4 to 5 µg/kg/day of aluminum (Ref. 20). FDA is considering whether to include in the previous warning a statement regarding the maximum daily aluminum intake recommended for patients. FDA believes such a recommendation would assist health care professionals in determining whether patients are receiving toxic levels of aluminum. For example, a health care professional administering per day 150 mL of an LVP solution containing 25 µg/L of aluminum to a patient also receiving 20 mL of drug A containing 2 µg/L of aluminum, 2 mL of drug B containing 100 µg/L of aluminum, and 10 mL of drug C containing 400 µg/L of aluminum, would be able to determine that the patient was receiving a total of 7.99 µg/day of aluminum (calculated (0.150 x 25) + (0.020 x 2) + (0.002 x 100) + (0.010 x 400)). The health care professional could then calculate the patient's intake level based on the patient's weight. If the patient weighed 2 kg, the patient would be receiving

[1] The agency has determined that most currently marketed LVP drug products contain less than 25 µg/L of aluminum (Ref. 17). Although aluminum content varied widely among different components and the same chemicals could have a different aluminum content depending on the manufacturer, lot to lot similarity for a specific chemical from a given supplier was found. LVP and SVP products from several manufacturers were tested. All LVP's tested, except one product, were less than 25 µg/L. FDA also bases this level on a considerable amount of stability data submitted to the agency over several years for LVP drug products.

approximately 4 μg/kg/day of aluminum (calculated 7.99 μg/2 kg).

FDA is specifically seeking comment on whether adding the language ''Patients should receive no more thatn 4 to 5 μg/kg/day of aluminum'' to the warning statement is appropriate. In addition, FDA is seeking comment on whether a 4 to 5 μg/kg/day level is reasonable and whether the proposed level is adequate to protect the public health.

Proposed § 201.323(e) would require that applicants and manufacturers develop validated assay methods to determine the aluminum content in parenteral drug products. The assay methods would be required to comply with current good manufacturing practice (CGMP) regulations under part 211 (21 CFR part 211) (see § 211.194(a)). Holders of approved applications for LVP's used in TPN therapy and SVP's used as additives in TPN solutions would be required to submit a supplement to FDA under § 314.70(c) (21 CFR 314.70(c)) describing the assay method used for determining the aluminum content. Under the proposed rule, applicants would submit the validation method used and the release data for several batches. Manufacturers of parenteral drug products not subject to an approved application would be expected to make assay methodology available to FDA during inspections.

Proposed § 201.323 would apply to all human drug LVP's, SVP's, and pharmacy bulk packages used in TPN. Licensed biological products are not covered by the proposal.

FDA is also considering codifying the language now proposed for § 201.323(a) and (e); however, when this language becomes final it may be in subpart E of part 310. These sections would limit the aluminum content for all LVP's used in TPN therapy to 25 μg/L for liquids and would require that applicants and manufacturers develop validated assay methods to determine the aluminum content in parenteral drug products.

III. Comments on the Notice of Intent

FDA received 11 comments on the notice of intent from professional associations, prescription drug manufacturers, a hospital, and a university. Most comments supported the proposed limit for aluminum content in LVP's and the labeling requirement for SVP's and pharmacy bulk packages. Four comments suggested changes to the proposed warning statement. A summary of the comments received and the agency's response follows.

A. Drug Products Susceptible to Aluminum Contamination

1. The notice of intent applied to all human drug LVP's and SVP's and pharmacy bulk packages used in TPN therapy. One comment contended that nutritional LVP's and nutritional LVP pharmacy bulk packages should be considered separate from SVP's and SVP pharmacy bulk packages. The comment stated that manufacturers of nutritional LVP products, which include amino acids, dextrose concentrations, and lipid emulsions, have already taken steps to contain aluminum levels through manufacturing processes and testing. Another comment suggested that any proposed regulation should apply only to nutritional parenterals and not other drug products.

The agency has concluded that, based on the available data and information concerning toxicity resulting from the presence of aluminum in parenteral drug products, it is necessary to regulate nutritional LVP's and LVP pharmacy bulk packages as well as nutritional SVP's and SVP pharmacy bulk packages. The proposal would establish a 25 μg/L limit for LVP's used in TPN therapy, and would require that the 25 μg/L limit be stated in the package insert of all LVP's used in TPN therapy. The proposal would also require that the maximum level of aluminum at expiry be stated on the immediate container label of SVP's and pharmacy bulk packages used in the preparation of TPN solutions.

The agency agrees that aluminum toxicity is a concern only for parenterals used in TPN therapy, and advises that the proposed limit for LVP's and the labeling requirement for LVP's, SVP's, and pharmacy bulk packages would only apply to LVP's used in TPN therapy and SVP's and pharmacy bulk packages used in the preparation of TPN solutions. The proposed rule would not apply to LVP's, SVP's, or pharmacy bulk packages not used in TPN therapy.

B. Patient Populations at Risk

In the notice of intent, the agency stated that it was especially concerned about three groups of patients at risk for aluminum toxicity: (1) Patients with kidney failure on chronic hemodialysis or continuous ambulatory peritoneal dialysis; (2) patients of any age receiving long-term TPN therapy, especially those with compromised kidney function; and (3) premature and full-term neonates who require TPN therapy.

2. One comment agreed with FDA's selection of the three groups most at risk, while another comment preferred to limit the regulation to premature infants and uremic patients receiving parenteral nutrition. Another comment suggested that the agency should first conduct indepth studies on aluminum toxicity in TPN patients, as well as studies of other populations at risk, such as the elderly, before proposing which groups to regulate.

The agency has considered these comments and the literature concerning the patient populations at risk and proposes to apply the regulation to products used for patients on TPN therapy who have impaired kidney function. Aluminum may accumulate to toxic levels after prolonged administration if kidney function is impaired, particularly if patients are exposed to other sources of aluminum, such as antacids, or if there is a greater than usual requirement for certain parenteral nutrition solutions that have a relatively high aluminum content, such as calcium and phosphate solutions. This includes patients with impaired kidney function receiving long-term parenteral nutrition and neonates receiving total parenteral nutrition. Premature neonates would be included because of their immature kidneys, their higher intake of fluids per unit body weight, and their greater need for calcium and phosphate solutions, which may be heavily contaminated with aluminum.

3. One comment stated that only long-term therapy with TPN solutions containing a high level of aluminum has led to clinically significant toxicity. Another comment stated that aluminum in TPN solutions is a problem for premature infants but not for patients receiving continuous ambulatory peritoneal dialysis, except from aluminum-containing phosphate gels. The comment added that patients with kidney disease who are not undergoing dialysis, but who are receiving TPN therapy, accumulate aluminum even when using crystalline amino acids. Another comment stated that 5-year followup studies of infants on TPN therapy revealed no aluminum loading, and short-term therapy had no long-term effects.

The agency disagrees that the only patients at risk are those on long-term therapy with TPN solutions that contain high levels of aluminum. The agency advises that the available research has shown that all patients with impaired kidney function on short-term or long-term TPN therapy are at risk. The agency also disagrees that 5-year studies have revealed no aluminum loading in infants. Again, the available literature provides sufficient evidence of toxic aluminum loading in infants who

receive TPN therapy (Refs. 2, 5, 6, and 8 through 13).

C. Sources of Aluminum Contamination

In the notice of intent, the agency stated that aluminum is usually found in parenteral drug products as a contaminant and is not added deliberately to the drug product. The notice also stated that although the drug substance is the main source of aluminum contamination in parenteral drug products, it is also leached from glass containers and closures during autoclaving and storage. The notice stated that additives are the major contributor of aluminum in TPN solutions, and that requiring the disclosure of aluminum levels in commonly used additives would permit the preparation of parenteral solutions lower in aluminum for high-risk patients.

4. One comment agreed that the sources of aluminum in parenteral drug products include raw materials and the glass final container. The comment stated that appropriate changes in specifications of raw materials would alleviate the problem.

Another comment stated that aluminum contamination results from three main sources: (l) Pharmaceutical ingredients (phosphates, gluceptates, gluconates, and some amino acids); (2) the container/closure system (aluminum content leached from glass container and rubber closures increases with shelf life); and (3) the manufacturing process (autoclave sterilization and membranes). The comment stated that technology does not exist to lessen the presence of aluminum.

The agency advises that changes in processing and screening of raw materials would significantly reduce aluminum contamination of parenteral drug products. The agency is proposing to require that the aluminum content be stated on the immediate container label of SVP's and pharmacy bulk packages so that the health professional preparing the TPN solution would be able to determine the aluminum content of the final solution. In addition, under the proposed rule, the package insert for all LVP's used in TPN therapy would state that the drug product contains no more than 25 µg/L. This would assist the practitioner when calculating the total amount of aluminum being administered to a patient with impaired kidney function receiving TPN therapy.

5. One comment suggested that FDA designate orphan drug status for parenterals used in infants to account for costs by manufacturers in complying with the aluminum content limits discussed in the notice of intent.

The Orphan Drug Act requires that Orphan Drug Designation be requested for individual drugs; therefore, the law would not permit designation of an entire class of drugs. However, new products intended for parenteral use in infants may fit the eligibility criteria for Orphan Designation and individual manufactures would be encouraged to apply. The Office of Orphan Products Development has a long history of encouraging manufacturers to apply for pediatric indications and would welcome applications for neonatal indications.

6. One comment suggested that FDA require parenterals to be packaged in plastic containers in order to lessen the aluminum leaching associated with glass containers.

The agency has decided not to require parenterals to be packaged only in plastic because not all products used for TPN therapy are available in plastic. Under the proposed regulation, health care professionals may choose an additive available in a plastic container for patients on TPN therapy. It is beyond the intent of this proposed rule to require that all drug products used in TPN therapy be packaged in plastic containers.

7. Three comments stated that deionized water has reduced the incidence of aluminum in parenteral solutions. One comment stated that following the U.S. Pharmacopeia proposed monograph for sterile water for dilution of hemodialysis concentrate would minimize aluminum toxicity problems. Aluminum toxicity would occur only in those patients where the aluminum loading exceeded dialysis capacity.

The agency advises that aluminum toxicity is not limited to patients undergoing dialysis treatment. Furthermore, although deionized water may reduce incidence of aluminum toxicity, the use of deionized water does not eliminate other sources of aluminum in TPN solutions.

8. Five comments argued that long-term TPN therapy using products containing crystalline amino acids, rather than casein hydrolysates, lessens toxic aluminum accumulation.

Although the agency agrees that replacement of casein hydrolysates with crystalline amino acids has reduced the levels of aluminum in LVP's, the agency believes that establishing a maximum level of aluminum in LVP's used for TPN therapy will contribute to decreasing the total amount of aluminum in these solutions. In addition, the proposed labeling requirement will permit calculation of total daily aluminum intake from all sources.

D. Units of Measure of Aluminum Content

In the notice of intent, the agency stated that a standard unit of measurement (i.e., parts per billion (ppb), parts per million, milligrams, or micrograms) should be specified to avoid confusion and errors, and that the same unit of measure be used to specify the drug being administered, the amount of aluminum present, and the maximum exposure permitted each day. The agency recommended that both mass and molar concentrations be stated in the labeling.

9. Three of the eight comments addressing this issue supported the µg/L unit, and two suggested either micro moles per liter (µM/L) or ppb. Two comments recommended that the unit of measurement be expressed as ppb. Other suggestions included: ''ppb (µg/L),'' ''µM/L (µg/L),'' and ''(g/mL)'' (grams per milliliter). One comment specifically recommended ''µmoles/L'' as a primary unit and ''µg/L'' in parentheses.

The agency has considered these comments and is proposing µg/L as the unit of measure. The agency believes that a standard unit of measurement will allow health care professionals to tailor the parenteral solution to the needs of certain patients. In addition, the agency has chosen a unit of measurement by which the levels of aluminum administered to patients can be easily calculated.

E. Levels of Aluminum Content in LVP's

The agency stated in the notice of intent that it was considering setting an upper limit of 25 µg/L or 25 ppb for LVP's used in TPN therapy. This limit is based primarily on a calculation that an intake of 3 liters per day would result in a total exposure of under 100 µg per day, which was recommended at the 1986 FDA workshop as a safe daily burden for healthy individuals. This limit is also based on a study in which patients were treated with long-term TPN solutions (Ref. 18). In addition, information provided to the agency indicates that most currently marketed LVP drug products will meet this specification (Ref. 17). The notice solicited comments regarding acceptable levels for parenteral drug products that are not required to meet this specification, including continuous ambulatory peritoneal dialysis drug products, hemodialysis drug products, antibiotics, and other drug products marketed as LVP's. The notice also sought additional data and information

regarding both safe levels and unsafe levels of aluminum in LVP's.

10. Four comments supported this limit. One comment recommended using the following definitions of safe, unsafe, and toxic:

''Safe''—the amount of aluminum which when administered parenterally that will result in neither body or tissue loading nor tissue disease or dysfunction; ''unsafe''—the amount of aluminum which when administered parenterally will result in tissue loading but which cannot be definitively determined to produce tissue disease or dysfunction; and ''toxic''—the amount of aluminum which when administered parenterally will result in tissue loading and that can be directly associated with tissue disease or dysfunction.

The comment recommended that these terms be made known to physicians and pharmacists who prescribe or prepare TPN solutions to better estimate the risk of aluminum toxicity to the patient.

Proposed § 201.323(a) would place an upper limit of 25 µg/L for liquid LVP's used in TPN therapy. The agency is also proposing that the package insert for all LVP's used in TPN therapy state that the drug product contains no more than 25 µg/L. The agency has determined that it is unnecessary for the proposed regulation to prescribe levels that are ''safe,'' ''unsafe,'' and ''toxic.'' The agency believes that the proposed limit on aluminum content for LVP's, the package insert requirement for LVP's, and the immediate container label statement for SVP's and pharmacy bulk packages would enable the health care professional to determine which drug products are safe for each patient.

11. One comment stated that proposing a limit for only LVP's disregards the fact that SVP's and pharmacy bulk packages contribute a large amount of aluminum to TPN solutions. Another comment objected to the agency's proposal to require a 25 ppb limit on LVP's but only a label statement for SVP's because LVP's provide less than 100 ppb of aluminum whereas SVP's can provide over 100,000 ppb of aluminum.

The agency recognizes that SVP's and pharmacy bulk package additives, such as phosphate and calcium solutions, are a major source of aluminum toxicity in TPN therapy. However, although the risks associated with aluminum toxicity in patients receiving TPN therapy are known, an acceptable level of aluminum in SVP's and pharmacy bulk package additives has not yet been established.

FDA is proposing the labeling requirement for SVP's and pharmacy bulk packages to permit the health care professional administering the drug to calculate the total aluminum exposure the patient receives from multiple parenteral sources. This calculation is especially important because additives appear to be the major contributor of aluminum to TPN solutions. Requiring the disclosure of the maximum level of aluminum present at expiry in SVP's and pharmacy bulk packages would also allow the user to make appropriate substitutions to prepare ''low aluminum'' parenteral solutions for use in patients who are in high-risk groups. The user would be unable to make accurate calculations of total aluminum exposure if the labeling of SVP's stated only a safe upper limit for aluminum rather than stating the exact or maximum amount of aluminum actually present.

12. One comment stated that proper methodology and test procedures should be established before an upper limit for the level of aluminum in LVP's can be set. Several comments stated that the proposed limit was not feasible for the following reasons: (1) It would be very difficult to get accuracy and reproducibility at such a low level; (2) suppliers of raw materials cannot readily reduce the level of aluminum in raw materials and no simple analytical method or technology for aluminum determination exists that could be performed outside of a research laboratory at detection levels below 100 ppb; (3) aluminum is a universal ingredient in essentially all materials, including those compounds where there is no practical technique to remove the aluminum; (4) some ingredients may leach significant amounts of aluminum from the glass containers and/or stoppers used for packaging, processing, and storage; (5) technology does not currently exist to prevent parenterals with electrolytes or a high pH from accumulating a higher aluminum level after autoclaving or to prevent filter membranes from introducing aluminum into a parenteral solution; (6) the limit appears too low for currently available methodology to measure with a consistent result in a manufacturing quality controlled environment; and (7) environmental contamination, such as dust particles that may contain over 2,000 ppb of aluminum, low levels of aluminum in the purest laboratory reagents, and leaching from laboratory supplies, can be a significant source of test variation.

Two comments recommended that FDA should alternatively require a limit of 100 ppb or 100 µg/L. One comment stated that there is essentially no practical risk of adverse health effects at 100 ppb. The comment suggested that, as an alternative to a proposed limit, LVP's used for nutritional support should include a labeling statement as follows: ''Use of this product typically provides not more than 100 ppb (µg/L) of aluminum. Use of this product, and any other additives, should be carefully undertaken if aluminum levels are of concern with the patient.''

One comment stated that because LVP's usually contain less than 100 ppb at expiration, FDA should not require release testing of every lot or establish an upper limit.

One comment stated that the 25 ppb limit would severely restrict availability of products in the LVP market, on which critically ill patients depend and for which no other acceptable nutritional alternative exists.

The agency disagrees with these comments. Technology exists to detect aluminum levels below 100 ppb and there is a risk of adverse health effects with aluminum levels at 100 ppb. The agency has determined that a specification of 100 µg/L could unnecessarily increase the aluminum content of TPN solutions. Increased levels of aluminum contamination may result in toxic accumulation of aluminum in human tissues. Aluminum intoxication may lead to fracturing osteomalacia, encephalopathy, microcytic hypochromic anemia, bone disease, and other serious illnesses (Ref. 8). The agency believes that the proposed limit of 25 µg/L is feasible and is necessary for the safe and effective use of LVP's in TPN therapy (Refs. 18 and 19). The agency emphasizes that the proposed limit is only applicable to LVP's involved in TPN therapy.

Although the proposed limit of 25 µg/L applies to all LVP's used in TPN therapy, the agency is identifying the following LVP's that are commonly used for prolonged TPN therapy, as those where high concentrations of aluminum toxicity are most likely to occur: Parenteral amino acid solutions, concentrated dextrose solutions, parenteral lipid emulsions, saline and electrolyte solutions, and sterile water for injection.

F. Aluminum Content Labeling for SVP's and Pharmacy Bulk Packages

In the notice of intent, FDA stated that it was considering requiring the immediate container labels for each lot of certain SVP's and pharmacy bulk packages to state the exact amount of aluminum present at the time of release, or alternately, the maximum amount of aluminum present. The notice stated that this labeling requirement would only apply to solutions intended for use and identified by the agency as being commonly used in the preparation of TPN solutions, and to all regularly used additives (e.g., vitamins, minerals, and

trace elements), regardless of aluminum levels detected. The notice stated that the agency is considering this approach for SVP's and pharmacy bulk packages to permit the person administering the drug to calculate the total aluminum exposure the patient receives from multiple parenteral sources.

13. Several comments supported a limit on the aluminum content of SVP's. One comment recommended that the agency should establish upper limits of allowable aluminum content in the near future on the basis of lowest aluminum concentrations measured in recently published literature. The comment suggested that such limits should reduce overall aluminum intake and should be achievable. In addition, the comment claimed that the regulation should encourage manufacturers to reduce the aluminum content of this class of products even further than a proposed upper limit and encourage hospital pharmacists to use additives lowest in aluminum concentration.

The agency has considered the comments and has decided not to propose a limit for the aluminum content of SVP's because, among other reasons, an acceptable level of aluminum in SVP and pharmacy bulk package additives has not yet been established. The proposed rule would require that the maximum level of aluminum present at expiry be stated on the immediate container label of all SVP's and pharmacy bulk packages used in the preparation of TPN solutions. This maximum level of aluminum must be expressed as: (1) The highest level for the batches produced during the last 3 years; (2) the highest level for the latest five batches; or (3) the maximum historical level, but only until completion of production of the first five batches after the rule takes effect. Although techniques for the analysis of aluminum at the 25 μg/L level exist, the proposed rule would not require that a specification for SVP's or pharmacy bulk packages be set at this time.

14. One comment noted that if no alternatives are available, it may be necessary to keep certain SVP's on the market even if they exceed the proposed limit. Another comment suggested that manufacturers of SVP's should have the opportunity to survey the aluminum content of their products before the agency determines the amount of aluminum in SVP's and the economic impact of this requirement.

The agency is not proposing a limit for SVP's in this rulemaking. Therefore, it will not be necessary to remove any SVP's from the market due to this proposed rule, nor will it be necessary for manufacturers of SVP's to survey the aluminum content of their products.

15. Several comments suggested that a list of drug products or components that are commonly used in the preparation of TPN solutions should include the salts of calcium, phosphate, and magnesium; trace element solutions; multivitamin preparations; and heparin solutions. One comment suggested that the products involved include parenteral trace minerals, parenteral multivitamins, and parenteral electrolyte supplements.

Another comment stated that the agency should determine what products would require aluminum content labeling from the product's use. The comment stated that many publications specify the aluminum level in products used for TPN therapy and for administration to the patient populations at risk cited by the agency.

Based on these comments, the agency has decided to broaden the labeling requirement stated in the notice of intent to apply to all SVP's used in TPN therapy. In an effort to assist manufacturers, the agency is identifying the following SVP's as those commonly used in the preparation of TPN solutions (this list may not be inclusive): Parenteral electrolyte solutions such as calcium chloride, calcium gluceptate, calcium gluconate, magnesium sulfate, potassium acetate, potassium chloride, potassium phosphate, sodium acetate, sodium lactate, and sodium phosphate; multiple electrolyte additive solutions; parenteral multivitamin solutions; single-entity parenteral vitamin solutions such as vitamin K injection, folic acid, cyanocobalamin, and thiamine; and trace mineral solutions such as chromium, copper, iron, manganese, selenium, and zinc.

16. Five comments agreed with the statement in the notice of intent that the immediate container labels of each lot of certain SVP's and pharmacy bulk packages must state the exact amount of aluminum present at the time of release. One comment stated that the requirement should apply to each of the SVP's listed in the response to comment 16 and in all additive solutions that may contribute to the total aluminum content of large volume solutions.

One comment, which opposed the labeling requirement for SVP's, stated that the requirement would not reduce aluminum toxicity and that compliance would be difficult. The comment asserted that stating the aluminum content at release does not accurately measure aluminum intake by the patient because some additives scavenge additional aluminum from glass packaging during shelf life. The comment also stated that the required labels could not be printed until the product is manufactured and testing is completed, and that this would be inconsistent with the agency's encouragement of straight-line filling and labeling of injectable products to prevent label mixups. The comment stated that the analytical technology is not practical for routine release testing in the laboratory because stringent control of aluminum contamination would be necessary, which would require well-trained, experienced personnel in a research setting. As an alternative, the comment suggested that the package insert state the potential for aluminum toxicity in certain patient populations and provide a range of aluminum content in the product that would allow the pharmacist or the physician to calculate patient risk based on approximate aluminum content in TPN solutions.

Although it is true that some additives scavenge additional aluminum from glass packaging during shelf life, the amount scavenged from various sources is generally very small compared with the aluminum contamination present in SVP's. In addition, many SVP's are available in plastic containers, for which scavenging is nominal. In regard to labeling, the agency is not suggesting a change from straight-line filling. The proposed rule would not require any change to the procedures now employed, since applicants and manufacturers may use historical levels of aluminum in their labeling. The use of historical data precludes the need for routine release testing. It is true that conducting the analytical test will require trained, experienced analysts, since all reagents, solvents, and apparatus need to be free of aluminum contamination. However, the technology exists and has been adapted by a number of manufacturers from which FDA has received data for LVP's over the years. Small manufacturers without the facility, equipment, or personnel can contract the testing out.

Accordingly, the agency has determined that proposed § 201.323(c) should require that the immediate container label of all marketed SVP's used as additives in TPN therapy state the maximum level of aluminum at expiry, rather than a range.

G. Aluminum Content/Assay Methods and Validation

In the notice of intent, the agency asked for comments on whether applicants should develop their own validated assay methods and submit them to FDA for approval. The notice

stated that the criteria to be considered in the selection of an aluminum release assay method would include accuracy, sensitivity, specificity, and reproducibility when applied to each of the tested drug products. In addition, the notice stated that an aluminum assay method should be validated by normal scientific procedures. For parenteral drugs that are the subject of an approved application, supplements must be submitted to provide the assay methodology to FDA for approval. The notice also recommended consultation of the agency's ''Guideline for Submitting Samples and Analytical Data for Methods Validation'' for assistance.

17. Two comments suggested that FDA provide the appropriate methodology to measure aluminum content. One comment stated that assay methodology only has a precision of about ±10 percent. One comment was concerned with the accuracy in measurement if 25 ppb is the upper limit, and suggested that FDA wait for methodology to be established before setting a limit. Another comment stated that the method of analysis should not be specified in the regulation, but that each applicant or manufacturer demonstrate under CGMP's that the method employed is precise and accurate. The comment noted that equipment essential for compliance with an assay methodology for periodic analytical testing would be feasible within a research laboratory but could not be operated within a manufacturing quality assurance laboratory.

Two comments recommended an assay methodology consisting of flameless or electrothermal atomic absorption spectroscopy or inductively coupled plasma emission spectroscopy. Manufacturers would establish either an in-house method or would contract with a laboratory. The comments also recommended that FDA issue specific procedures to ensure that manufacturers use appropriate control procedures.

FDA has considered the comments and has concluded that, under proposed § 201.323(e), applicants would have the discretion and flexibility to develop their own validated assay methods, but would be required to submit them to FDA for approval. As required under 21 CFR 314.50(e)(2)(i), the method of analysis must include a description of each sample; the proposed regulatory specifications for the drug; a detailed description of the methods of analysis; supporting validation data for accuracy, specificity, precision, and ruggedness; and complete results of the applicant's tests on each sample. Manufacturers must maintain records for examination by FDA during inspections.

Approved application holders for LVP's and SVP's used in TPN therapy must submit a supplement under § 314.70(c) that describes the method used for determining aluminum content. Validation methods, release data, and historical data at expiry for several batches should be submitted. For SVP's not subject to approved applications, manufacturers are expected to maintain records for examination by FDA during inspections.

18. One comment recommended that the graphite furnace atomic absorption method that is used for a quantitative determination of aluminum in parenteral products should be adopted by FDA as an industry standard assay method. Another comment recommended graphite furnace atomic absorption spectrophotometry with Zeeman background correction as an industry standard.

The agency declines to accept the comments' suggestions. As stated, the choice is left to applicants and manufacturers to select and properly validate an appropriate methodology.

19. One comment recommended in determining a limit for aluminum in parenteral drugs that the analytical methodology should be capable of determining aluminum content in complex matrices, that adherence to CGMP's and appropriate documentation should be sufficient for compliance, and that routine batch testing should not be required.

The agency disagrees. Strict adherence to CGMP's, instead of routine batch testing, will not fully address the issue of aluminum contamination. Routine batch testing is important under the proposed rule because the applicants and manufacturers of SVP's and pharmacy bulk packages will be expected to assay sufficient lots of products to establish the maximum historical level of aluminum present at the expiry. The applicant or manufacturer would be expected to monitor the aluminum level of their product at the time of release and through the expiry of their product.

20. Another comment stated that an engineering study for an assessment of 40 to 60 raw material aluminum analyses would cost approximately $150,000 and require 700 man-hours for each plant, and a second study for sampling and testing of 25 to 30 unit operations for all 24 individual amino acid processes would require a $1.5 million commitment. The comment stated further that the cost of implementation of aluminum control measures could easily exceed $20 million, and continuing costs of analyses and process control could be $1 million per year.

FDA disagrees with the comment's cost estimates. FDA estimates that the annualized cost to amino acid suppliers would be $1,416,622. This figure includes the first year or one-time costs that the comment estimates at $20 million. In addition, FDA notes that the cost of compliance represents a small percentage of amino acid revenue. Amino acid sales were $1.6 billion in 1996 and are projected to grow at an annual rate of 9 percent. ''Commercial Amino Acids,'' *Chemical Business Newsbase* (May 23, 1997). The annualized cost of compliance for amino acid suppliers represents just .09 percent of the 1996 annual amino acid sales. FDA considers this an acceptable cost.

H. Warning Statement for LVP's and SVP's

In the notice of intent, FDA stated that it is considering requiring the package insert for LVP's to contain a warning statement about the potential aluminum toxicity of TPN mixtures.

21. One comment suggested that LVP products bear a warning statement as follows: ''Use of this product typically provides not more than 100 ppb (µg/L) of aluminum. Use of this product, and any other additives, should be carefully undertaken if aluminum levels are of concern with the patient * * *.'' Another comment recommended that the package insert for LVP's used in TPN state: ''Typically may contain up to 100 ppb (mcg/L) of aluminum.'' In addition, the comment stated that the package insert for SVP's should state that the potential for aluminum toxicity exists in certain patient populations, and that a range of aluminum content should be provided.

Another comment recommended that the package insert of LVP's and SVP's state that the product:

> ''contains aluminum of a given quantity which, when given in conjunction with other additives as part of a parenteral nutrition solution, may result in accumulation of aluminum in bone and other tissues and may contribute to the pathogenesis of bone disease.''

The comment also suggested that a special warning be given to uremic patients receiving these additives. The warning would state: ''The cumulative amount of aluminum administered from this and other intravenous additives may cause encephalopathy as well as bone disease. Safe amounts of aluminum intake have not been established for uremic patients.''

FDA has determined that, under proposed § 201.323(d), the package

insert for LVP's and SVP's must contain the following warning statement about aluminum toxicity in patients receiving TPN therapy:

WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

The agency has considered the data submitted in response to the notice of intent and other available data, and has concluded that a specification of 100 μg/L is unnecessarily high for LVP's. In addition, the agency believes that indicating a range for aluminum content of SVP's would not provide health care professionals with enough information to calculate the aluminum content of the final TPN solution.

In response to the comment that the proposed rule should include a warning statement to uremic patients receiving additives in TPN solutions, the agency advises that it examined aluminum toxicity in different patient populations and has concluded that the warning statement should apply not only to uremic patients but also to all patients with impaired kidney function and neonates receiving TPN therapy.

22. One comment suggested that the effects of aluminum on individuals should be examined in terms of aluminum intake per kg of body weight rather than absolute aluminum intake since an adult and infant receiving identical quantities of aluminum would have a vastly different body burden of aluminum.

The agency has considered the option of examining the effects of aluminum on individuals in terms of aluminum intake per kg of body weight, but has tentatively concluded that setting a limit for LVP's and requiring the labeling statement for SVP's would be the best method to measure aluminum intake. However, as discussed previously, FDA is seeking comment on including language in the warning statement concerning maximum aluminum intake per kg of body weight.

IV. Legal Authority

FDA's proposal to regulate the aluminum content of certain parenteral drug products and to require aluminum content to be stated in the labeling of certain drug products is authorized by the Federal Food, Drug, and Cosmetic Act (the act). Section 502(a) of the act (21 U.S.C. 352(a)) prohibits false or misleading labeling of drugs, including, under section 201(n) of the act (21 U.S.C. 321(n)), failure to reveal material facts relating to potential consequences under customary conditions of use. Section 502(f) of the act requires drug labeling to have adequate directions for use, adequate warnings against use by patients where its use may be dangerous to health, as well as adequate warnings against unsafe dosage or methods or duration of administration, as necessary to protect users. In addition, section 502(j) of the act prohibits the use of drugs that are dangerous to health when used in the manner suggested in their labeling. Drug products that do not meet the requirements of section 502 of the act are deemed to be misbranded.

In addition to the misbranding provisions, the premarket approval provisions of the act authorize FDA to require that prescription drug labeling provide the practitioner with adequate information to permit safe and effective use of the drug product. Under section 505 of the act (21 U.S.C. 355), FDA will approve a new drug application (NDA) only if the drug is shown to be both safe and effective for its intended use under the conditions set forth in the drug's labeling. Section 701(a) of the act (21 U.S.C. 371(a)) authorizes FDA to issue regulations for the efficient enforcement of the act.

Under part 201 (21 CFR part 201) in § 201.100(d) of FDA's labeling regulations, prescription drug products must bear labeling that contains adequate information under which licensed practitioners can use the drugs safely and for their intended purposes. Section 201.57 describes specific categories of information, including information for drug use in selected subgroups of the general population and warnings on adverse reactions and potential safety hazards that must be present to meet the requirements of § 201.100. In addition, under 21 CFR 314.125, an NDA will not be approved unless there is adequate safety and effectiveness information for the labeled uses and the product complies with the requirements of part 201.

If the proposed rule is finalized, any drug product not in compliance with § 201.323 would be considered to be misbranded under section 502 of the act and an unapproved new drug under section 505 of the act.

V. Proposed Implementation Plan

FDA proposes that any final rule that may issue based on this proposal become effective 1 year after its date of publication in the **Federal Register**. After that date, NDA's submitted under § 314.50 and abbreviated new drug applications (ANDA's) submitted under 21 CFR 314.94 would have to comply with the labeling requirements under proposed § 201.323. Holders of approved NDA's or ANDA's would meet the requirements of proposed § 201.323 by submitting supplements under § 314.70 or § 314.97 (21 CFR 314.97). Applicants for LVP's used in TPN therapy and SVP's used as additives in TPN solutions would also be required to submit a supplement under § 314.70(c) that describes the assay method for determining the aluminum content. Applicants must submit 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 would submit an amendment under 21 CFR 314.60 or 314.96.

VI. Request for Comments

Interested persons may, on or before April 6, 1998, submit to the Dockets Management Branch written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. FDA is specifically seeking comments on whether adding the language ''Patients should receive no more than 4 to 5 μg/kg/day of aluminum'' to the warning statement is appropriate, and whether a 4 to 5 μg/kg/day level is reasonable and adequate to protect the public health.

VII. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order.

Based on a study conducted for the agency by the Eastern Research Group (ERG), a private consulting firm, FDA has determined the annual costs of the proposed regulation to the affected industries. FDA estimates total annualized compliance costs at $20.1

million. This estimate is composed of one-time costs annualized to $9.8 million at a 7 percent discount rate and recurring annual costs of $10.3 million. Over 50 percent of the total costs are due to actions undertaken to manufacture LVP solutions and their inputs that comply with the aluminum requirements. One alternative that would have required SVP's to be labeled with the actual aluminum content of each batch would have raised these costs (Ref. 21).

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. The ERG report presents estimated compliance costs by type of establishment. The report demonstrates that the largest compliance costs will be incurred by amino acid suppliers at about $1.4 million per establishment, followed by manufacturers of LVP's at about $320,000 per establishment, and other suppliers to TPN manufacturers at $134,000 per establishment. The data used in this analysis further show, however, that very few of the companies involved in these manufacturing activities are considered small by the standards of the Small Business Administration. Therefore, the agency certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities and, under the Regulatory Flexibility Act, no further analysis is required.

VIII. The Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). Therefore, in accordance with 44 U.S.C. 3506(c)(2)(B) and 5 CFR part 1320, FDA is providing the following title, description, and respondent description of the information collection contained in this proposal, along with an estimate of the resulting annual collection of information burden. This estimate includes the time needed for reviewing instructions, gathering and maintaining the data needed, and completing and reviewing the collection of information.

With respect to the following collection of information, FDA invites comments on: (1) Whether the proposed collection of information is necessary for proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition

Description: FDA is proposing to amend its regulations to add certain labeling requirements concerning aluminum in LVP's and SVP's used in TPN. FDA is also proposing to specify an upper limit of aluminum permitted in LVP's and to require applicants and manufacturers to develop and to submit to FDA for approval validated assay methods for determining aluminum content in parenteral drug products.

Description of Respondents: Persons and businesses, including small businesses and manufacturers.

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN

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

There are no capital costs or operating and maintenance costs associated with this collection of information.

The agency has submitted a copy of the proposed rule to OMB for its review and approval of this information collection. Interested persons are requested to send comments regarding this information collection to the Office of Information and Regulatory Affairs, OMB (address above).

IX. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Alfrey, A. C., ''Aluminum,'' *Advances in Clinical Chemistry*, 23:69–91, 1983.

2. Kerr, D. N. S. et al., ''Aluminum-induced Dialysis Osteodystrophy: The Demise of 'Newcastle Bone Disease'?'' *Kidney International*, 29 (Suppl. 18):S–58–64, 1986.

3. Sedman, A. B. et al., ''Evidence of Aluminum Loading in Infants Receiving Intravenous Therapy,'' *The New England Journal of Medicine*, 312:1337–1343, 1985.

4. Koo, W. W. K. et al., ''Aluminum Contamination of Infant Formulas,'' *Journal of Parenteral and Enteral Nutrition*, 12:170–173, 1988.

5. Sedman, A. B. et al., ''Encephalopathy in Childhood Secondary to Aluminum Toxicity,'' *The Journal of Pediatrics*, 105:836–838, 1984.

6. American Academy of Pediatrics Committee on Nutrition, ''Aluminum Toxicity in Infants and Children,'' *Pediatrics*, 78:1150–1154, 1986.

7. Vargas, J. H. et al., ''Metabolic Bone Disease of Total Parenteral Nutrition: Course after Changing from Casein Amino Acids in Parenteral Solutions with Reduced Aluminum Content,'' *American Journal of Clinical Nutrition*, 48:1070–1078, 1988.

8. Klein, G., ''Aluminum in Parenteral Products: Medical Perspective on Large and Small Volume Parenterals,'' *Journal of Parenteral Science and Technology*, 43:120–124, 1989.

9. ASCN/ASPEN Working Group on Standards for Aluminum Content of Parenteral Nutrition Solutions, ''Parenteral Drug Products Containing Aluminum as an Ingredient or a Contaminant: Response to FDA Notice of Intent and Request for Information,'' *American Journal of Clinical Nutrition*, 53:399–402, 1991.

10. Andreoli, S. P., J. A. Smith, and J. M. Bergstein, ''Aluminum Bone Disease in Children: Radiographic Features from Diagnosis to Resolution,'' *Radiology*, 156:663–667, 1985.

11. McGraw, M. et al., ''Aluminum Content of Milk Formulae and Intravenous Fluids Used in Infants,'' *The Lancet*, 1:157, 1986.

12. Puntis, J. W. L., K. Hall, and I. W. Booth, ''Plasma Aluminum and Prolonged Parenteral Nutrition in Infancy,'' *The Lancet*, 2:1332–1333, 1986.

13. Koo, W. W. K. et al., ''Response to Aluminum in Parenteral Nutrition During Infancy,'' *Journal of Pediatrics*, 109:877–883, 1986.

14. Greger, J. L., and M. J. Baier, ''Excretion and Retention of Low or Moderate Levels of Aluminum by Human Subjects,'' *Food and Chemical Toxicology*, 21:473–477, 1983.

15. Gorsky, J. E. et al., ''Metabolic Balance of Aluminum Studied in Six Men,'' *Clinical Chemistry*, 25:1739–1743, 1979.

16. Bishop, N. J. et al., ''Increased Concentration of Aluminum in the Brain of an Infant,'' *Archives of Disease in Childhood*, 64:1316–1317, 1989.

17. Koo, W. W. K. et al.,''Aluminum in Parenteral Nutrition Solution—Sources and Possible Alternatives,'' *Journal of Parental and Enteral Nutrition*, 10:591–595, 1986.

18. Heyman, M. B. et al., ''Aluminum Does Not Accumulate in Teenagers and Adults on Prolonged Parenteral Nutrition Containing Free Amino Acids,'' *Journal of Parenteral and Enteral Nutrition*, 10:86–87, 1986.

19. Klein, G. L., ''Unusual Sources of Aluminum,'' in *Aluminum and Renal Failure*, edited by M. E. Debroe and J. W. Coburn, Kluwer, Boston, 1989.

20. Bishop, N. J. et al., ''Aluminum Neurotoxicity in Preterm Infants Receiving Intravenous Feeding Solutions,'' *New England Journal of Medicine*, 336:1557–1561, 1997.

21. Eastern Research Group, *Compliance Cost Analysis of a Regulation for Parenteral Drug Products Containing Aluminum*, March 11, 1996.

22. March 3, 1986, Meeting Minutes for the Advisory Committee on Endocrinologic and Metabolic Drug Products.

23. November 6, 1986, Meeting Minutes for Public Workshop on aluminum toxicity in clinical medicine, existing aluminum monitoring, clinical effects of aluminum loading, and methodology for quantitative aluminum determination in parenteral products.

24. June 25 and 26, 1987, Meeting Minutes of the Allergenic Products Advisory Committee—available in Docket No. 84N–0387.

List of Subjects in 21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 201 be amended as follows:

PART 201—LABELING

1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 358, 360, 360b, 360gg–360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

2. New § 201.323 is added to subpart G to read as follows:

§ 201.323 Aluminum in large and small volume parenterals used in total parenteral nutrition.

(a) The aluminum content of all large volume parenteral (LVP) drug products used in total parenteral nutrition (TPN) therapy shall not exceed 25 micrograms per liter (µg/L).

(b) The package insert of all LVP's used in TPN therapy shall state that the drug product contains no more than 25 µg/L. This information shall be contained in the ''Precautions'' section of the labeling of all LVP's used in TPN therapy.

(c) The maximum level of aluminum present at expiry shall be stated on the immediate container label of all small volume parenteral (SVP) drug products and pharmacy bulk packages used in the preparation of TPN solutions. The aluminum content shall be stated as follows: ''Contains no more than _____ µg/L.'' The immediate container label of all SVP drug products and pharmacy bulk packages that are lyophilized powders used in the preparation of TPN solutions shall contain the following statement: ''When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than _____ µg/L.'' This maximum level of aluminum shall be stated as the highest of:

(1) The highest level for the batches produced during the last 3 years;

(2) The highest level for the latest five batches; or

(3) The maximum historical level, but only until completion of production of the first five batches after this rule takes effect.

(d) The package insert for all LVP's, SVP's, and pharmacy bulk packages shall contain the following warning statement, intended for patients with impaired kidney function and for neonates receiving TPN therapy. This information shall be contained in the ''Warnings'' section of the labeling of all SVP's and LVP's as follows:

WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

(e) Applicants and manufacturers shall develop validated assay methods to determine the aluminum content in parenteral drug products. The assay methods shall comply with current good manufacturing practice requirements. Applicants shall submit to the Food and Drug Administration (FDA) both validation of the method used and release data for several batches. Manufacturers of parenteral drug products not subject to an approved application shall make assay methodology available to FDA during inspections. Holders of pending applications shall submit an amendment under § 314.60 or § 314.96 of this chapter.

Dated: December 5, 1997.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 98–76 Filed 1-2-98; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF THE INTERIOR

Minerals Management Service

30 CFR Chapter II

Workshops on The Federal Oil and Gas Royalty Simplification and Fairness Act of 1996 (RSFA)

AGENCY: Minerals Management Service, Interior.

ACTION: Notice of workshop.

SUMMARY: The Minerals Management Service (MMS), Royalty Management Program, is implementing the requirements of the Federal Oil and Gas Royalty Simplification and Fairness Act of 1996. The purpose of this notice is to inform the public of a public workshop session on assessing for chronic erroneous reporting.

DATES: The workshop will be held on Tuesday, January 27, 1998, from 2 p.m. until 4 p.m., Mountain time.

ADDRESSES: The workshop will be held at the Embassy Suites Denver Southeast, 7525 East Hampden Avenue, Denver, Colorado 80231, telephone (303) 696–6644. Mail comments to: David S. Guzy, Chief, Rules and Publications Staff, Royalty Management Program, Minerals Management Service, P.O. Box 25165, MS 3021, Denver, Colorado 80225–0165; courier delivery to building 85, Denver Federal Center, Denver, Colorado 80225; or e-mail David__Guzy@mms.gov.

FOR FURTHER INFORMATION CONTACT: David S. Guzy, Chief, Rules and Publications Staff, telephone (303) 231–3432; Fax (303) 231–3385; e-mail: David__Guzy@mms.gov.

SUPPLEMENTARY INFORMATION: President Clinton signed the Federal Oil and Gas Royalty Simplification and Fairness Act (RSFA) on August 13, 1996, to improve the management of royalties from Federal oil and gas leases. This is the first major legislation affecting royalty management since the Federal Oil and Gas Royalty Management Act of 1982 (FOGRMA) was passed in January 1983.

In our **Federal Register** Notice dated October 30, 1996 (61 FR 55941), MMS listed key issues involved in implementing RSFA. This workshop will focus on assessing for chronic erroneous reporting and will follow and