rule that was published in the **Federal Register** on January 10, 2000, (65 FR 1309), Airspace Docket No. 99–ASO–27.

EFFECTIVE DATE: January 26, 2000.

FOR FURTHER INFORMATION CONTACT: Nancy B. Shelton, Manager, Airspace Branch, Air Traffic Division, Federal Aviation Administration, P.O. Box 20636, Atlanta, Georgia 30320; telephone (404) 305–5627.

SUPPLEMENTARY INFORMATION:

History

Federal Register Document DOCID: fr10ja00–6, Airspace Docket No. 99–ASO–27, published on January 10, 2000, (65 FR 1309), amended Class D surface area airspace at Jacksonville Whitehouse NOLF, FL. An error was discovered in the amendatory language identifying the airspace description. This action corrects that error.

Correction to Final Rule

Accordingly, pursuant to the authority delegated to me, the publication for describing Jacksonville Whitehouse NOLF, FL, Class D surface area airspace at Jacksonville Whitehouse NOLF, FL, as published in the **Federal Register** on January 10, 2000, (65 FR 1309), (**Federal Register** Document DOCID: fr10ja00–6; page 1309), is corrected as follows:

Section 71.1 [Corrected]

* * * * *

ASO FL D Jacksonville Whitehouse NOLF, FL [Corrected]

By removing "be effective during the specific dates and times established in advance by a Notice to"

* * * * *

Issued in College Park, Georgia, on January 10, 2000.

Nancy B. Shelton,

Acting Manager, Air Traffic Division, Southern Region.

[FR Doc. 00–1815 Filed 1–25–00; 8:45 am]

BILLING CODE 4910–13–M

DEPARTMENT OF TRANSPORTATION

Federal Aviation Administration

14 CFR Part 71

[Airspace Docket No. 99–ANE–92]

Establishment of Class E Airspace; Burlington, VT

AGENCY: Federal Aviation Administration (FAA), DOT.

ACTION: Direct final rule; correction; confirmation of effective date.

SUMMARY: This notice confirms the effective date of a direct final rule that establishes Class E airspace area at Burlington, VT (KBTV) to provide for adequate controlled airspace for aircraft executing instrument approaches to the Burlington International Airport at times when the Burlington Air Traffic Control Tower is closed. This action also corrects a typographical error in the docket number and changes the longitude and latitude of the Burlington International Airport to reflect North American Datum (NAD) 1983.

EFFECTIVE DATE: The direct final rule published at 64 FR 68008 is effective 0901 UTC, February 24, 2000.

FOR FURTHER INFORMATION CONTACT: David T. Bayley, Air Traffic Division, Airspace Branch, ANE–520.3, Federal Aviation Administration, 12 New England Executive Park, Burlington, MA 01803–5299; telephone (781) 238–7586; fax (781) 238–7596.

SUPPLEMENTARY INFORMATION:

The FAA published this direct final rule with a request for comments in the **Federal Register** on December 6, 1999 (64 FR 68008). The FAA uses the direct final rulemaking procedure for a non-controversial rule where the FAA believes that there will be no adverse public comment. This direct final rule advised the public that no adverse comments were anticipated, and that unless a written adverse comment, or a written notice of intent to submit such an adverse comment, were received within the comment period, the regulation would become effective on February 24, 2000. No adverse comments were received, and thus this notice confirms that this direct final rule will become effective on that date.

This direct final rule also corrects the docket number for this action to 99–ANE–92. The docket number used for the publication of the direct final rule was previously used for another airspace action. That other action, however, was issued from FAA Headquarters, while this action was issued from the New England Region. Therefore, the FAA has determined that the error in the docket number caused no confusion to interested persons wishing to comment on this proposal and corrects the docket number in this action.

Lastly, the longitude and latitude coordinates published in the direct final rule must be updated to reflect North American Datum (NAD) 1983. The FAA has determined that neither of these corrections expands the scope of the direct final rule.

Correction to the Direct Final Rule

Accordingly, pursuant to the authority delegated to me, the establishment of Class E airspace at Burlington, VT as published in the **Federal Register** on December 6, 1999 (64 FR 68008), **Federal Register** document 99–31518: page 68009, column 2; and the description in FAA Order 7400.9G, dated September 1, 1999, and effective September 16, 1999, which is incorporated by reference in 14 CFR 71.7; are corrected to read as follows:

Subpart E—Class E Airspace

* * * * **

Paragraph 6002—Class E Airspace Areas Designated as Extending Upward From the Surface of the Earth

* * * * **

ANE VT E2 Burlington, VT [New]

Burlington International Airport, VT (Lat. 44°28′23″ N, long. 73°09′01″ W.)

Within a 5-mile radius of Burlington International Airport. This Class E airspace is effective during the specific dates and times established in advance by a Notice to Airman. The effective dates and times will thereafter be continuously published in the Airport/Facility Directory.

* * * * *

Issued in Burlington, MA, on January 13, 2000.

William C. Yuknewicz,

Acting Manager, Air Traffic Division, New England Region.

[FR Doc. 00–1814 Filed 1–25–00 8:45 am]

BILLING CODE 4910–13–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. 90N–0056]

RIN 0910–AA74

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations to add certain labeling requirements for aluminum content in large volume parenterals (LVP's), small

volume parenterals (SVP's), and pharmacy bulk packages (PBP's) used in total parenteral nutrition (TPN). FDA is also specifying an upper limit of aluminum permitted in LVP's and requiring applicants to submit to FDA validated assay methods for determining aluminum content in parenteral drug products. The agency is adding 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.

DATES: This rule is effective January 26, 2001.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

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

FDA published a notice of intent in the **Federal Register** on May 21, 1990 (55 FR 20799) announcing FDA's concerns about toxic aluminum levels in TPN and requesting comments. As a result of the comments received, on January 5, 1998, FDA published a proposed rule in the **Federal Register** (63 FR 176) in which it proposed 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 PBP's used in the preparation of TPN solutions; (4) require that the package insert of all LVP's and SVP's, including PBP's, 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 used in TPN therapy and submit the validated assay methods to FDA for approval.

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. FDA included specific references in the proposed rule that supported the following information about aluminum toxicity (63 FR 176). Research indicates that neonates and patient populations with impaired kidney function may be at high risk of exposure to unsafe amounts of aluminum. Many drug products used routinely for TPN 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 it is deposited in human tissues.

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

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 neonates receiving TPN therapy. 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.

FDA received 21 comments on the proposed rule and addresses each of those comments in section III of this document. FDA is adopting this final rule as described below. The agency has also made minor edits to the final rule in response to the President's June 1, 1998, memorandum on plain language in Government writing.

II. Highlights of the Final Rule

FDA is implementing this final rule because of evidence linking the use of parenteral drug products containing aluminum to morbidity and mortality among patients on TPN therapy, especially premature neonates and patients with impaired kidney function.

The new regulations added to part 201 ((21 CFR 201) at § 201.323(a)) limit the aluminum content for all LVP's used in TPN therapy to 25 micrograms per liter (µg/L). This requirement applies 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.

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

New § 201.323(c) requires the product's maximum level of aluminum at expiry to be stated on the immediate container label of SVP's and PBP's used in the preparation of TPN solutions. The statement on the immediate container label must read as follows: "Contains no more than —— µg/L of aluminum." For those SVP's and PBP's 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 must 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 January 26, 2001. The labeling requirement applies to all SVP's and PBP'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.

New § 201.323(d) requires the package insert for all LVP's, SVP's, and PBP's used in TPN to contain a warning statement. The warning statement must be included in the "Warnings" section of the labeling. The warning must 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.

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 µg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

FDA removed the phrase "intended for patients with impaired kidney function and for neonates receiving TPN therapy" from the first sentence of § 201.323(d) because the phrase duplicated information contained in the actual warning and because the phrase made the first sentence of § 201.323(d) unclear.

New § 201.323(e) requires applicants and manufacturers to use validated assay methods to determine the aluminum content in parenteral drug products used in TPN therapy. The assay methods must comply with current good manufacturing practice regulations under part 211 (21 CFR part 211) (see § 211.194(a)). Holders of approved applications for LVP's, SVP's, and PBP's used in TPN therapy are required to submit a supplement to FDA under § 314.70(c) (21 CFR 314.70(c); see also 21 U.S.C. 356a(b)) describing the assay method used for determining the aluminum content. Applicants must submit the validation method used and the release data for several batches. In addition, manufacturers of parenteral drug products not subject to an approved application must make assay methodology available to FDA during inspections (see 21 CFR 211.160 and 211.180(c)).

New § 201.323 applies to all human drug LVP's, SVP's, and PBP's used in TPN. Licensed biological products are not covered by this rule.

III. Comments on the Proposed Rule

FDA received 21 comments on the proposed rule from professional associations, prescription drug manufacturers, Congress, individuals on TPN, and a hospital. Most comments supported the proposed limit for aluminum content in LVP's and the labeling requirement for SVP's and PBP's. Four comments suggested changes to the proposed warning statement. A summary of the comments received and the agency's responses follow.

A. Levels of Aluminum Content in LVP's

The agency stated in the proposed rule that it was considering setting an upper limit of 25 µg/L for LVP's used in TPN therapy. 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. The agency also proposed that the package insert for all LVP's used in TPN therapy state that the drug product contains no more than 25 µg/L.

1. Fifteen comments strongly supported a limit on aluminum of 25 µg/L. Two of the comments specifically supported the accompanying proposal that the package insert state that the drug product contains no more than 25 µg/L of aluminum.

FDA agrees that 25 µg/L of aluminum is a reasonable limit. As stated in the proposed rule, the 25 µg/L limit is feasible and necessary for the safe and effective use of LVP's used in TPN therapy.

Two comments, one from an LVP manufacturer and the other from a trade association, stated that 25 µg/L is not a reasonable limit for the varying reasons outlined in comments 2 through 8, in section III. A of this document.

2. These comments stated that data from production batches show potential rejections of finished batches at release if a limit of 25 µg/L is adopted. One of these comments specified that more than 10 percent of assay results exceed the proposed limit. It also stated that their current batch analysis showed a 95 percent confidence that at least 99 percent of the batch contained less than 50.37 µg/L of aluminum at release.

FDA understands that not all current batches of LVP's will meet a 25 µg/L level of aluminum. FDA will implement this rule 1 year after the date of publication to allow companies an opportunity to meet the specifications in this rule. FDA is not adopting a higher level because FDA believes a 25 µg/L level of aluminum is necessary to protect the public health.

3. The same two comments said that glass leaching over time increases aluminum levels so that initial levels cannot be established low enough to ensure batch acceptability by the end of the expiry period.

The intention of this rule is to reduce aluminum to an acceptable level in TPN products. A manufacturer can reduce toxicity by any of several routes, including using containers made of different materials.

4. One of these comments requested that FDA set the maximum level of aluminum using the procedure specified in the draft guidance entitled "Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances" (draft Q6A guidance) (62 FR 62890). This draft guidance states that a limit on impurities can be determined by (1) Determining the level at which the impurity is present in relevant batches and then (2) determining the mean plus upper confidence limit for the impurity where the upper confidence limit is three times the standard deviation of batch analysis data.

FDA is not using the procedures specified in the draft Q6A guidance because it is not appropriate to use current product aluminum levels to determine upper limits when the goal is to reduce aluminum levels to at or below the limit defined as safe. Further, the guidances entitled "Q3A: Impurities in New Drug Substances," (January 1996) and "Q3B Impurities in New Drug Products," (November 1997) address the issue of quantification of impurities. These guidances state that limits should be set no higher than the level that can be justified by safety data. The guidances also state that, for impurities known to be unusually potent or to produce toxic or unexpected pharmacological effects, the quantitation and detection limit of the analytical methods should be commensurate with the level at which the impurities must be controlled. FDA's primary concern in enacting this rule is ensuring the safety of the patient population and limiting exposure to the impurity. FDA has determined that the 25 µg/L limit is necessary for the safe and effective use of LVP's in TPN therapy.

5. These comments also stated that current assay methods cannot reliably distinguish between 25 µg/L and 30 µg/L. The comment did not provide supporting data or evaluation of the specific methods claimed to lack the required accuracy.

FDA understands that methods are currently available that are capable of detecting aluminum concentrations at 25 µg/L levels. In particular, FDA is aware that graphite furnace atomic absorption spectrometometry can be a sufficiently accurate validation method. However, FDA will accept any validated analytical method to assay aluminum content in TPN.

6. One of these comments suggested that FDA should require labeling of LVP's with an average and a range of aluminum values at expiry, obtained from five production scale batches, instead of requiring a limit of 25 µg/L

of aluminum in LVP's. The labeling would state "Approximate average aluminum value— µg/L. Approximate aluminum range —— µg/L to — µg/L." The same comment requested that FDA apply the same labeling standards to LVP's, SVP's, and PBP's, under the rationale that some LVP's are identical in composition to PBP's.

FDA notes that if a manufacturer makes a PBP specifically for LVP use, the PBP should not contain more than 25 µg/L of aluminum so that the LVP manufactured from the PBP does not contain more than 25 µg/L of aluminum. FDA is implementing the 25 µg/L limit for LVP's rather than permitting an average or a range of aluminum levels to be stated for LVP's because the agency believes that it is more appropriate to set a maximum level due to the large volume of use of these products. FDA has determined that the 25 µg/L limit is necessary for the safe and effective use of LVP's used in TPN therapy. FDA's basis for not requiring SVP's and PBP's to be labeled with an average and a range of aluminum levels is discussed in response to comment 11 in section III. B of this document.

7. This same comment stated that establishing a 25 µg/L limit on LVP's would not have the desired effect of reducing aluminum levels in TPN because the majority of aluminum contamination is due to SVP's, not LVP's. A different comment requested that FDA narrow coverage of the rule to only those products that contribute significant amounts of aluminum to TPN: Calcium gluconate, calcium gluceptate, potassium phosphates, and sodium phosphates. The comment stated that calcium gluconate alone can contribute 88 percent of the total aluminum present in a TPN formulation.

FDA recognizes that numerous factors contribute to aluminum contamination in TPN therapy. Therefore, FDA is addressing the problem in several different ways in an effort to reduce aluminum contamination, rather than reducing aluminum from one source.

8. Another comment noted that the United States Pharmacopeia (USP) has limited aluminum levels in monographs for substances used in hemodialysis, including: Calcium acetate, calcium chloride, magnesium chloride, potassium chloride, sodium acetate, sodium bicarbonate, and sodium chloride. The comment stated that additional steps could be taken to limit aluminum levels in monographs of substances used in the manufacture of TPN solutions. Although FDA believes USP's limits add a valuable contribution to limiting aluminum contamination, FDA believes the additional measures set forth in this final rule are needed to prevent an unsafe level of aluminum in TPN.

B. Aluminum Levels in SVP's and PBP's

In the proposed rule, FDA proposed requiring that the maximum level of aluminum at expiry be stated on the immediate container label of SVP's and PBP's used in the preparation of TPN solutions. FDA proposed that the statement on the immediate container label read as follows: "Contains no more than —— µg/L of aluminum." For those SVP's and PBP's that are lyophilized powders used in the preparation of TPN solutions, FDA proposed that the maximum level of aluminum at expiry 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." FDA proposed that the maximum level of aluminum must 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.

9. Two comments supported FDA's proposal. One comment requested that FDA further specify limitations on aluminum content for SVP's.

FDA plans to implement the labeling requirements for SVP's and PBP's as proposed. FDA does not consider it appropriate to consider SVP's as a single category because SVP's are used for many indications other than TPN and in target populations where aluminum toxicity is not an issue.

10. One comment asked that FDA set a minimum level below which the amount of aluminum would not need to be declared.

FDA believes it is important for health care practitioners to know as much as possible about the aluminum levels being consumed by their patients. FDA believes the knowledge that a product has a low level of aluminum is just as important as the knowledge that a product contains high levels of aluminum. This labeling requirement permits health care professionals administering the drug to be able to calculate the total aluminum exposure the patient receives from multiple sources, and to be able to make appropriate substitutions to prepare "low aluminum" parenteral solutions for use in patients who are in high risk groups. Therefore, FDA believes all LVP's, SVP's, and PBP's used in TPN should be labeled with their aluminum levels.

11. One comment stated that information about the average amount of aluminum and its range at expiration for LVP's and SVP's is more useful than the maximum historical value at expiration, since otherwise a physician may overestimate the amount of aluminum being delivered to the patient. Another comment proposed that FDA require labeling of SVP's and PBP's with an average and a range of aluminum values at expiry, obtained from five production scale batches, such that the labeling would state "Approximate average aluminum value —— µg/L. Approximate aluminum range —— µg/L to—— µg/L."

The agency believes that information about the maximum concentration of aluminum potentially present at expiry is more useful to the practitioner. FDA's intention is to limit exposure to aluminum, and the use of average values or range at expiration would not achieve this goal as effectively.

C. Applicability to Biologics

In the proposed rule, FDA stated that licensed biological products were not covered by the proposal.

12. Twelve comments stated that biologics, specifically albumin, plasminate, and any other colloidal volume expanders, should be regulated. The Center for Biologics Evaluation and Research at the FDA is currently considering whether to regulate the levels of aluminum in licensed biological products. However, such regulation is outside the scope of this final rule.

D. Statement Regarding Maximum Intake of Aluminum

FDA proposed requiring a statement regarding the maximum daily aluminum intake recommended for patients. FDA sought comment on whether adding the language "Patients should receive no more than 4 to 5 µg/kg/day of aluminum" to the warning statement was appropriate and on whether a 4 to 5 µg/kilogram (kg)/day level is reasonable and adequate to protect the public health.

13. Two comments stated that FDA should include definitions of safe, unsafe, and toxic levels of aluminum. Three comments said that FDA should provide health professionals with a best estimate as to what constitutes a toxic aluminum load.

One comment stated that proposing to limit aluminum to 4 to 5 µg/kg/day would either make TPN formulations unavailable to neonates or expose doctors to liability, because it is a

difficult level to meet. Another comment said that 4 to 5 µg/kg/day is too low and may not allow patients to receive adequate amounts of calcium and phosphates. One comment noted that parenteral limits are much lower than oral limits, and expressed the belief that the proposed language did not offer guidance with respect to combined oral and parenteral daily limits. Another comment noted that the proposal does not provide a therapeutic alternative to too high aluminum levels, and asked that FDA include in the statement a definition of the populations truly at risk.

One comment stated that it would be difficult for health care professionals to calculate total aluminum intake, particularly for neonates receiving multiple intravenous infusions. Another comment stated that the factors that affect plasma aluminum clearance [1] can influence sensitivity to aluminum load [2] at any concentration of aluminum infused, and therefore aluminum concentration in TPN cannot be correlated directly to aluminum plasma levels.

Two comments recommended alternative statements. One suggested using the following language: "Daily parenteral intake of greater than 4 to 5 µg/kg/day of aluminum has been associated with central nervous system and bone toxicity." Another suggested using the following warning: "No aluminum toxicity to the brain or bone of premature neonates has been documented with intakes below 5 µg/kg/day; however, tissue loading may still occur at that rate of administration to preterm infants."

One comment requested that FDA require such a warning statement only for those SVP's for which aluminum is a significant problem.

Based on these comments, FDA revised the warning to include a statement on current findings rather than a statement about maximum safe levels. FDA included specific references in the proposed rule (63 FR 176).

E. Acceptable Assay Methods for Determining Aluminum Levels

FDA proposed permitting applicants and manufacturers to have the discretion and flexibility to develop their own validated assay methods as long as the methods are in compliance with current good manufacturing practices requirements. Holders of approved applications for LVP's, SVP's and PBP's used in TPN therapy would be required to submit a supplement under part 314 (21 CFR part 314) in § 314.70(c) that described the method used for determining aluminum content. Holders of pending applications would be required to submit an amendment under § 314.60 or § 314.96. For SVP's not subject to approved applications, manufacturers would be required to maintain records for examination by FDA during inspections.

14. One comment stated that the USP provides an established system and procedure for the development of uniform analytical methods. The comment asked that FDA request that U.S.P. develop assay methods for determining aluminum content in parenterals rather than requiring individual companies to do so.

FDA believes that more than one analytical method may be suitable or necessary to assay aluminum content in different TPN products. Once FDA has reviewed several methods, it may evaluate whether it is appropriate to develop uniform analytical procedures. Individual companies may provide their validated analytical methods to USP for publication. Through this process, USP may establish a uniform analytical method for determining aluminum content in parenterals. FDA will accept any method that is validated and in compliance with current good manufacturing practice requirements.

15. One comment supported FDA's proposal. The comment also stated that analytical methods should be those in general use, such as flameless atomic absorption spectroscopy with a graphite furnace, and the method should be sufficiently sensitive to detect aluminum at the µg/L and not the milligram (mg) per liter level.

Again, FDA will accept any method that is validated and in compliance with current good manufacturing practice requirements. Any analytical method must be sensitive enough to detect aluminum at the µg/L and not the mg/L level, because the aluminum limits for LVP's and the required labeling statements for LVP's, SVP's, and PBP's are measured in µg/L.

F. Date of Implementation of the Final Rule

FDA proposed that any final rule that issued based on its proposed rule would become effective 1 year after the final rule's date of publication in the **Federal Register**. After that date, new drug applications (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 new requirements under § 201.323.

16. One comment proposed an implementation date of 4 years after publication of the final rule in the **Federal Register** to account for the time necessary to collect and analyze data. Another comment suggested an implementation date of 31/2 years after publication of the final rule, or whenever data from five batches of product became available and the supplement was approved. This comment stated that the additional time is necessary to collect aluminum levels at expiry by an appropriate and validated method, since companies do not presently have such data.

Under the final rule, a manufacturer may use: (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. This means that if expiry data under (1) and (2) of comment 16 in section III. F of this document are not available within 1 year, data available for the product during that year can be used under (3) of comment 16. As a manufacturer accrues additional data, it can then also use methods (1) and/or (2) of comment 16.

17. One comment asked whether FDA expects supplements to be submitted and approved and labeling changed within 1 year of publication of the final rule, or simply for supplements to be submitted within 1 year of publication of the final rule.

FDA expects supplements to be submitted and labeling to be changed within 1 year of publication of this final rule. Under current regulations (§ 314.70(c)) and the Food and Drug Administration Modernization Act of 1997 (21 U.S.C. 356a(b)), a manufacturer can file a changes being effected supplement for immediate implementation of this change. Thus, FDA believes implementation should take place in 1 year.

G. Cost of Implementing the Rule

FDA estimated in the proposed rule that the annualized cost to amino acid suppliers to implement the proposed rule would be $1,416,622. This figure includes first year or one-time costs estimated at $20 million.

18. One comment stated that wholesale raw material amino acids for intravenous use is a fraction of the $109 million market cited by FDA, and is actually much closer to $40 million. The comment went on to state that this market is shrinking and will continue to

[1] The clearance rate for aluminum is the rate at which aluminum is removed from the body by normal body functioning.

[2] Aluminum load is the amount of aluminum in the body.

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