

OMB # 0910-0439
Docket # 90N-0056
Expires 04/30/03

OMB INFORMATION COLLECTION - SUPPORTING STATEMENT

**ALUMINUM IN LARGE AND SMALL VOLUME PARENTERALS
USED IN TOTAL PARENTERAL NUTRITION - 21 CFR 201.323**

Justification

1. Circumstances of Information Collection

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 total parenteral nutrition therapy. Research indicates that neonates and patient populations with impaired kidney function may be at high risk of exposure to unsafe amounts of aluminum. Studies show that aluminum may accumulate in the bone, urine, and plasma of infants receiving TPN. Many drug products used routinely in parenteral therapy may contain levels of aluminum sufficiently high to cause clinical manifestations. Generally, when medication and nutrition are administered orally, the gastrointestinal tract acts as an efficient barrier to the absorption of aluminum, and relatively little ingested aluminum actually reaches body tissues. However, parenterally administered drug products containing aluminum bypass the protective mechanism of the gastrointestinal tract and aluminum circulates and is deposited in human tissues. Aluminum toxicity

is difficult to identify in infants because few reliable techniques are available to evaluate bone metabolism in premature infants. Techniques used to evaluate the effects of aluminum on bone in adults cannot be used in premature infants. Although aluminum toxicity is not commonly detected clinically, it can be serious in selected patient populations, such as neonates, and may be more common than is recognized.

FDA 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 parental nutrition (TPN). FDA is 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 requirement because of evidence linking the use of parenteral drug products containing aluminum to morbidity and mortality among patients on TPN therapy, especially among premature neonates and patients with impaired kidney function.

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

21 CFR 201.323(b) Requires that the package insert of all large volume parenterals used in total parenteral nutrition therapy state that the drug product contains no more than 25 µg/L. This information must be contained in the "Precautions" section of the labeling of all

large volume parenterals used in total parenteral nutrition therapy.

- 21 CFR 201.323(c) Requires that the maximum level of aluminum present at expiry be stated on the immediate container label of all small volume parenteral drug products and pharmacy bulk packages used in the preparation of total parenteral nutrition solutions. The aluminum content must be stated as prescribed in the regulation. The immediate container label of all small volume parenteral drug products and pharmacy bulk packages that are lyophilized powders used in the preparation of total parenteral nutrition solutions must contain a statement prescribed in the regulation.
- 21 CFR 201.323(d) Requires that the package insert for all large volume parenterals, small volume parenterals, and pharmacy bulk packages contain a warning statement, prescribed in the regulation, intended for patients with impaired kidney function and for neonates receiving total parenteral nutrition therapy. This information must be contained in the "Warnings" section of the labeling of all small volume parenterals and large volume parenterals.
- 21 CFR 201.323(e) Requires that applicants and manufacturers develop validated assay methods to determine the aluminum content in parenteral drug products. The assay methods must comply with current good manufacturing practice requirements. Applicants must submit to FDA both validation of the method used and release data for several batches. Manufacturers of parenteral drug products not subject to an approved application must make assay methodology available to FDA during inspections. Holders of pending applications must submit an amendment to the application.

2. Purpose and Use of Information

These requirements are necessary 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.

The regulation of the aluminum content of certain parenteral drug products and the requirement to state the aluminum content 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 prohibits false or misleading labeling of drugs, including, under section 201(n) of the act, 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, FDA will approve a new drug application 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.

Under 21 CFR 201 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, which must be present. 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.

3. Use of Improved Information Technology

In the mid-1980's, FDA began working with pharmaceutical sponsors to develop Computer-Assisted New Drug Applications (CANDA). CANDAs were designed to provide information (text, data, image) electronically to facilitate the review of applications (including related submissions such as revised labeling). These efforts yielded valuable information but were limited because for each new drug review division sponsors tended to develop different hardware and software approaches. A reviewer might be confronted with an array of hardware, software, and review tools to conduct a review that differed between sponsors and applications. Also, CANDAs were never approved as a substitute for the archival copy, so firms were still required to

submit copies.

One solution to limitations of CANDAs was an approach whereby staff responsible for a particular review discipline (eg, chemistry, clinical) worked directly with pharmaceutical sponsors to develop a consistent approach that would be applicable to all sponsors and to all review divisions. Focus on this approach has evolved into the Electronic Regulatory Submission and Review (ERSR) Program. This new initiative is intended to ensure both the electronic availability of information and the means to manipulate this information electronically to yield a review.

ERSR has been made possible by other developments. The harmonization of FDA Form 356h has ensured that NDAs, ANDAs, and Biological License Applications would contain comparable information in the same sections of the submission. The promulgation of the "Electronic Records; Electronic Signatures" final rule allowed FDA to accept electronic submissions without an accompanying paper archival copy because electronic records are equivalent to paper records and electronic signatures are equivalent to hand-written signatures provided the requirements of 21 CFR Part 11 are met and the document has been identified in the agency's public docket as being acceptable for filing. The Guidance for Industry on "Archiving Submissions in Electronic Format - NDAs" provides for the receipt and archival of electronic report forms and tabulations. Another guidance for industry on "Providing Regulatory Submissions in Electronic Format - NDAs" issued in January 1999.

ERSR is made up of a variety of projects that are in different stages of development and implementation. These projects are categorized into 3 areas: First, "Electronic Submissions" includes standards-related projects to define the format and content of regulatory submissions; written guidance for industry to follow in preparing electronic submissions; an Electronic Document Room project to accommodate the receipt, archive, and storage of electronic transmissions; an Electronic Gateway project to provide an agency-level central point for receipt of secure electronic transmissions and routing to the Centers; and scientific databases that include structured databases, reference guides, and analytical tools used by reviewers. Second, "Corporate Databases, Documentbases and Applications" includes projects under the Electronic Document Management System and the Management Information System. Third, other electronic initiatives including technical infrastructure, technical support, and training.

ERSR will impact the underlying business processes related to regulatory submissions and reviews. Document rooms will handle electronic media rather than paper copies. Reviewers will review submissions online and generate their review documents online. Reviewers will conduct data analysis using structured databases, which combine data extracted from the submission under review as well as historical data from earlier submissions. Industry sponsors and manufacturers will experience reduced paper costs and manpower to compile paper submissions and better access

to application status information through electronic mail.

4. Efforts to Identify Duplication

Because of the unique nature of the information to be collected, duplication of information is unlikely.

5. Involvement of Small Entities

If a rule has a significant impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize the significant economic impact of such a rule on small entities. In the proposed rule, FDA relied on the estimated compliance costs by type of establishment as projected by Eastern Research Group. That analysis determined that very few of the affected companies are considered small by the standards of the Small Business Administration. Therefore, the agency certified that the proposed rule would not have a significant economic impact on a substantial number of small entities.

The agency received no comments specifically directed at this certification. Nevertheless, due to comments on other aspects of its estimates and modifications to the original analysis, FDA, in the final rule, reanalyzed the small business impacts of the final rule.

Fewer than 8 of the 24 companies identified in the ERG report as a manufacturer or supplier of TPN products or their

inputs are small businesses according to the Small Business Administration (SBA) definitions. It is possible that four SVP manufacturers are small under the SBA definitions. However, since the average annualized cost for these establishments is estimated at about \$51,000 each, the estimated annualized compliance costs for these companies are expected to account for less than one percent of their annual revenues. FDA further identified one amino acid supplier that may be a small business; but again, the annualized compliance costs for this firm would be less than 1 percent of annual revenues. The size of one dextrose supplier and one electrolyte supplier could not be confidently determined due to the scarcity of data. Therefore, it was not possible to determine whether the compliance costs of these firms would represent more than 1 percent of their revenues. Based on the very few small firms that might incur a significant impact, The Commissioner certifies under § 605(b) of the Regulatory Flexibility Act that the final rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

6. Consequences if Information Collected Less Frequently

As discussed above, these requirements are necessary 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.

7. Consistency with the Guidelines in 5 CFR 1320.5(d)(2)

The collection methods are consistent with the guidelines of 5 CFR 1320.5(d)(2), except that applicants are required to submit 12 copies of labeling to FDA under the supplement regulations in 21 CFR 314.70. This is necessary to facilitate FDA review of these supplements in a timely manner. This is already approved by OMB under Control Number 0910-0001.

8. Consultation Outside the Agency

In developing the proposed rule, FDA 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. 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.

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. 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: (1) 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. 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 responses were discussed in the proposed rule.

On January 5, 1998, FDA published the proposed rule (FR Vol. 63 176) requesting comments on the proposed collections of

information and received 21 comments 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 are discussed in the final rule.

9. Remuneration of Respondents

FDA has not provided and has no intention to provide any payment or gift to respondents under this provision.

10. Assurance of Confidentiality

Trade secret information collected under section 505 of the act is protected by statute and regulation (21 U.S.C. 331(j) and 21 CFR part 20).

11. Questions of a Sensitive Nature

This rulemaking does not contain questions pertaining to sex, behavior, attitude, religious beliefs, or any other matters that are commonly considered private or sensitive in nature.

12. Estimates of Annualized Hour Burden

FDA is amending its regulations to add certain labeling requirements for aluminum content in LVP's, SVP's and PBP's used in TPN. FDA is also specifying an upper limit of aluminum permitted in LVP's and requiring manufacturers to submit to FDA for approval 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 premature neonates and patients with impaired kidney function.

Compliance with the information collection burdens under 21 CFR 201.323(b), (c), and (d) consists of submitting application supplements to FDA containing the revised labeling for each product. This burden is minimized by the fact that the regulation prescribes many of the labeling statements that must be included in the labeling. Compliance with the information collection burden under 21 CFR 201.323(e) consists of submitting validation of the method used and release data to FDA.

Based on data concerning the number of applications for LVP's, SVP's, and PBP's used in TPN received by the agency, FDA estimates that the labeling for approximately 200 products will be changed under section 201.323(b), (c), and (d). FDA estimates that it will take approximately 14 hours to prepare and submit to FDA each labeling change. Based on data collected by the Eastern Research Group (see Ref. 1 of final rule) concerning the number

of affected manufacturers, FDA estimates that approximately 65 respondents will each submit one validated assay method annually under section 201.323(e). FDA estimates that it will take approximately 14 hours to prepare and submit to FDA each validated assay.

Section 201.323(e) states that manufacturers of parenteral drug products not subject to an approved application must make assay methodology available to FDA during inspections, as required in part 211. FDA has submitted the recordkeeping requirements included in part 211 to OMB for approval (64 FR 19180, April 19, 1999). Therefore, this requirement is not estimated in the table below.

Section 201.323(e) also states that holders of pending applications must submit an amendment under § 314.60 or § 314.96 of this chapter. Recordkeeping requirements included in part 314 are approved by OMB until November 3, 2001, under OMB control number 0910-0001. Therefore, this requirement is not estimated below.

The burdens can be charted as follows:

| Estimated Annual Reporting Burden ¹ | | | | | |
|--|-----------------------|-------------------------------|------------------------|--------------------|-------------|
| 21 CFR Section | Number of Respondents | Annual Frequency per Response | Total Annual Responses | Hours per Response | Total Hours |
| 201.323 (b), (c) and (d) | 200 | 1 | 200 | 14 | 2,800 |
| 201.323 (e) | 65 | 1 | 65 | 14 | 910 |

TOTAL

3,710

¹ There are no capital costs or operating and maintenance costs associated with this collection.

13. Estimates of Annualized Cost Burden to Respondents

FDA's Economic's Staff estimates the average hourly wage for program personnel involved in complying with the reporting requirements to be \$33.00. Multiplying the estimated average hourly wage by 1.5 to account for non-wage labor costs, an estimated hourly labor cost is \$50.00. The estimated total cost to the respondents for submitting the required labeling and assay information, using \$50.00 as the hourly cost figure, is \$185,500 (3710 x \$50).

14. Estimates of Annualized Cost Burden to the Government

No additional equipment or staff will be required to review the additional information. The required information will be submitted in an application or supplement to the appropriate reviewing division within FDA for review by personnel with an estimated wage rate of \$26.00 per hour. Assuming an overhead rate of 60 percent, the cost to FDA is about \$42.00 per hour. A required review would take approximately 25 hours per application, on average. Thus, total FDA cost to review these submissions is approximately \$278,250 (265 x 25 x \$42).

15. Changes in Burden

This is a new paperwork collection.

16. Publication of Information Collection Results

There are no tabulated results to publish for this information collection.

17. Display of Expiration Date for OMB Approval

No FDA forms are associated with this collection of information.

18. Exceptions to Certification Statement

There are no exceptions requested in this information collection.

praalumf.ss 8/28/97; revised 8/27/99; 8/30/99