from 700 feet AGL is needed to accommodate the SIAP. Class E airspace designations for airspace areas extending upward from 700 feet or more above the surface are published in Paragraph 6005 of FAA Order 7400.9J, dated August 31, 2001, and effective September 16, 2001, which is incorporated by reference in 14 CFR 71.1. The Class E airspace designation listed in this document would be published subsequently in the Order.

The FAA has determined that this proposed regulation only involves an established body of technical regulations for which frequent and routine amendments are necessary to keep them operationally current. Therefore, this proposed regulation—(1) is not a ''significant regulatory action'' under Executive Order 12866; (2) is not a ''significant rule'' under DOT Regulatory Policies and Procedures (44 FR 11034; February 26, 1979); and (3) does not warrant preparation of a regulatory evaluation as the anticipated impact is so minimal. Since this is a routine matter that would only affect air traffic procedure and air navigation, it is certified that this proposed rule would not have significant economic impact on a substantial number of small entities under the criteria of the Regulatory Flexibility Act.

List of Subjects in 14 CFR Part 71

Airspace, Incorporation by reference, Navigation (air).

The Proposed Amendment

In consideration of the foregoing, the Federal Aviation Administration proposes to amend 14 CFR part 71 as follows:

PART 71—[AMENDED]

1. The authority citation for 14 CFR part 71 continues to read as follows:

Authority: 49 U.S.C. 106(g), 40103, 40113, 40120; EO 10854, 24 FR 9565, 3 CFR, 1959–1963 Comp., p. 389.

§ 71.1 [Amended]

2. The incorporation by reference in 14 CFR 71.1 of Federal Aviation Administration Order 7400.9J, dated August 31, 2001, and effective September 16, 2001, is proposed to be amended as follows:

Paragraph 6005 Class E airspace areas extending upward from 700 feet or more above the surface of the earth.

AEA MD E5, Annapolis [New]

Lee Airport
(Lat. 38°56′34″ N., long. 76°34′06″ W.)

That airspace extending upward from 700 feet above the surface within a 6.2 mile radius of the Lee Airport, Annapolis, MD.

Issued in Jamaica, New York, on March 28, 2002.

Richard J. Ducharme,

Assistant Manager, Air Traffic Division, Eastern Region.

[FR Doc. 02–11055 Filed 5–2–02; 8:45 am]

BILLING CODE 4910–13–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 314 and 601

[Docket No. 00N–1652]

RIN 0910–AB91

Requirements for Submission of Labeling for Human Prescription Drugs and Biologics in Electronic Format

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its regulations governing the format in which certain labeling is required to be submitted for review with new drug applications (NDAs), certain biological license applications (BLAs), abbreviated new drug applications (ANDAs), supplements, and annual reports. The proposal would require that certain labeling content be submitted electronically in a form that FDA can process, review, and archive. Submitting the content of labeling in electronic format would simplify the drug labeling review process and speed up the approval of labeling changes.

DATES: Submit written or electronic comments by August 1, 2002. Submit written comments on the information collection requirements by June 3, 2002. See section X of this document for the proposed effective date of a final rule based on this document.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.fda.gov/dockets/ecomments. Submit written comments on the information collection provisions 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: Stuart Shapiro, Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT:

Randy Levin, Center for Drug Evaluation and Research (HFD–1), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5411, or
Robert A. Yetter, Center for Biologics Evaluation and Research (HFM–10), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, 301–827–0373.

SUPPLEMENTARY INFORMATION:

I. Background

A. Current Labeling Submission Requirements

Section § 314.50 (21 CFR 314.50) of our (FDA's) current regulations describes the content and format requirements for NDAs. Under § 314.50(e)(2)(ii), an applicant is required to submit, in the archival copy of an application, copies of the label and all labeling for the drug product. Under § 314.50(l)(1), information in the archival copy required under § 314.50(a) (i.e., the application form, including the signature of the applicant) and § 314.50(e) (i.e., samples and labeling) must be submitted to the agency on paper, while other required information may be submitted either on paper or on microfiche (or another suitable microform system, if FDA and the applicant agree). Under § 314.71(b) (21 CFR 314.71(b)), supplements to approved applications submitted to the agency under § 314.70 (21 CFR 314.70) must follow the procedures described in § 314.50. In addition, § 314.81(b)(2)(iii) (21 CFR 314.81(b)(2)(iii)) requires that ''currently used professional labeling, patient brochures, or package inserts'' be submitted with annual reports.

Section § 314.94 (21 CFR 314.94) sets forth requirements for the content and format of ANDAs. Under § 314.94(a)(8)(ii), the archival copy of an ANDA must include copies of the label and all labeling for the drug product. Under § 314.94(d), an applicant may submit all or portions of the archival copy of an ANDA in any form that FDA and the applicant agree is acceptable. Under § 314.97 (21 CFR 314.97), supplements and other changes to approved ANDAs must be submitted to the agency under the requirements of §§ 314.70 and 314.71. As noted previously, under § 314.71(b), supplements to approved applications submitted to the agency under 314.70 must follow the procedures described in § 314.50. Finally, under § 314.98(c) (21 CFR 314.98(c)), ANDA applicants must submit annual reports as required in § 314.81(b)(2)(iii).

Section § 601.2 (21 CFR 601.2) describes the requirements for submission of a BLA, which include the

requirement that specimens of enclosures and Medication Guides for a product, if any, be submitted. Section 601.12 (21 CFR 601.12) describes the requirements to make changes to an approved BLA, including labeling changes. Under § 601.12(f), labeling changes to a biological product approved under a BLA may generally only be made after the approval of a labeling supplement to the BLA, although certain types of labeling changes may be made before FDA approval of a supplement or by reporting the change in an annual report. Neither § 601.2 nor § 601.12 specifies a format in which the labeling or other information required in BLAs, BLA supplements, or annual reports must be submitted to FDA.

The term ''labeling'' used in §§ 314.50, 314.94, 314.81, and 601.12 is defined in section 201(m) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(m)) to mean both labels[1] and other written, printed, or graphic matter upon any article or any of its containers or wrappers, or accompanying such article. Thus, requiring the submission of ''labeling'' entails submission of the label (i.e., the label on the immediate container) and labeling. Labeling consists of the comprehensive prescription drug labeling directed to health care practitioners (i.e., the labeling required under § 201.100(d)(3) (21 CFR 201.100(d)(3)), commonly referred to as the ''package insert'' or ''professional labeling'') and other labeling.[2]

B. The Effect of the Proposed Rule on Current Submission Requirements

Under this proposal, applicants would be required to submit to us in electronic format the *content* of the package insert or professional labeling, including all text, tables, and figures. As explained below, this submission should be formatted in the manner described in agency guidance on electronic submissions.

This proposed requirement would be in addition to existing requirements, described in section I.A of this document, that copies of the label and labeling and specimens of enclosures be submitted. For example, *copies* of the package insert must still be submitted to us in an NDA under § 314.50(e)(2)(ii). Copies submitted to us must be identical to the label and labeling and specimens of enclosures that appear in the package insert, on the immediate container, or in any other form distributed. Under this proposal, these copies may be submitted electronically or on paper.

C. Electronic Format Submission Initiatives

In the **Federal Register** of March 20, 1997 (62 FR 13430), we published a regulation on electronic records and electronic signatures (part 11 (21 CFR part 11)). Part 11 generally provides that in instances where records are required to be submitted to the agency, such records may be submitted in electronic format instead of paper format, provided the controls in part 11 are met and we have identified the submission in the public docket as the type of submission we are prepared to accept in electronic format.

Although we have not up to this time required regulatory submissions in electronic format, we have issued guidances describing how to submit NDAs, BLAs, and other types of regulatory submissions in electronic format. In the **Federal Register** of January 28, 1999 (64 FR 4432), we announced the availability of a guidance entitled ''Providing Regulatory Submissions in Electronic Format—NDA's'' (the NDA electronic submission guidance), which provided information on how to submit a complete archival copy of an NDA in electronic format. The guidance applies to the submission of original NDAs, as well as to the submission of supplements and amendments to NDAs. Among other things, the NDA electronic submission guidance provides recommendations on how to submit ''labeling text'' in electronic format. ''Labeling text'' is the term used in the NDA electronic submission guidance to mean labeling required under § 201.100(d)(3), including all text, tables, and figures required by or included under authority of those sections. The term ''content of labeling,'' as used in this rulemaking, is intended to mean the same as the term ''labeling text,'' as used in the guidance. The NDA electronic submission guidance recommends that labeling text be submitted as a portable document format (PDF) file and that the file be submitted in the following format:

- The print area (i.e., the area of the PDF file when printed) should fit on an 8 1/2- by 11-inch sheet of paper with 1-inch margins;
- The page orientation should be portrait;
- The file should not contain any columns, headers, or footers; and
- The files should be paginated, beginning with page 1. The guidance also describes recommended font types and minimum font sizes for the PDF file text.

In November 1999, we published a guidance to assist applicants in submitting documents in electronic format for review and archive purposes as part of a BLA, product license application (PLA), or establishment license application (ELA) (64 FR 61647, November 12, 1999).

In January 1999, we issued a guidance on general considerations for electronic submissions entitled ''Providing Regulatory Submissions in Electronic Format—General Considerations'' (the general considerations guidance) (64 FR 4433, January 28, 1999). In the general considerations guidance, we include a description of the types of electronic file formats that we are able to accept to process, review, and archive electronic documents. The general considerations guidance states that documents submitted in electronic format should enable the user to: (1) Easily view a clear and legible copy of the information; (2) print each document page by page while maintaining fonts, special orientations, table formats, and page numbers; and (3) copy text and images electronically into common word processing documents. To achieve these and other goals, we recommend that all electronic documents be submitted as PDF files.

II. Rationale for Requiring Electronic Submission of the Content of Labeling

As discussed in section I of this document, until now, the initiatives we have undertaken have been focused on permitting, but not requiring, applicants to submit required regulatory documents in electronic format. For a number of reasons, we believe that it is important to require that the content of labeling (i.e., the labeling required under § 201.100(d)(3), including all text, tables, and figures) be submitted to us electronically for prescription drugs and biological products that are subject to the requirements of § 201.100(d)(3).

A. Why Is It Important for the Content of Labeling To Be Submitted Electronically?

Each year, we receive more than 1,000 proposed labeling changes for approved NDAs and BLAs, and more than 2,600 proposed original and supplemental labeling changes for ANDAs. As part of the review process, we conduct a word-for-word comparison of the proposed labeling with the last approved labeling

[1]Under section 201(k) of the act, the term ''label'' means a display of written, printed, or graphic matter upon the immediate container of any article.

[2]Section 201.100(d) requires that any labeling distributed by or on behalf of the manufacturer, packer, or distributor of the drug, that furnishes or purports to furnish information for use of the drug, or which prescribes, recommends, or suggests a dosage for the use of the drug, must meet the content and format requirements in 21 CFR 201.56 and 201.57.

to verify that all labeling changes have been identified. In addition, for ANDAs, we conduct a word-for-word comparison of the labeling for the proposed generic drug product and the reference listed drug to verify that any differences in labeling have been correctly annotated and explained by the ANDA applicant under § 314.94(a)(8)(iii). Currently, a reviewer must conduct these comparisons manually using two paper copies of the labeling. This manual comparison is slow and subject to error.

The proposed rule would require that the content of labeling be submitted in an electronic file in a form that we can process, review, and archive. The formatting of these submissions will allow electronic review and comparison of labeling files. We believe that the use of computer technology to identify changes in different versions of the labeling would greatly enhance the accuracy and speed of this part of the review. The ability to quickly identify changes in different versions of the labeling would shorten the time needed to approve labeling changes and reduce the amount of resources we need to devote to labeling review. Our ability to protect the public health will be enhanced because electronic review and comparison of labeling files will provide a higher degree of certainty that all portions of prescription drug labeling are appropriate. Furthermore, in certain circumstances (e.g., changes to NDA labeling made under § 314.70(c)), we review labeling changes after they have been implemented. We may find the revised labeling to be inappropriate. Our ability to quickly identify the changes and correct the labeling would minimize public exposure to the inappropriate labeling.

B. Why Should the Content of Labeling Be Submitted in PDF?

For the agency to efficiently use computer technology to identify changes between different versions of labeling, we need to receive labeling in an electronic file format that supports word-for-word comparisons of files and in a form we can process, review, and archive. Although there are several file formats and computer software applications capable of providing the functions necessary for review purposes, it would not be cost effective to purchase many different types or versions of software and train our employees to use them, or to archive many different file formats. At this time, PDF is the only type of electronic file format that we have the ability to use to process, review, and archive submissions.

We believe that of the file formats and software applications currently available, PDF best meets our needs while keeping costs to applicants low. Using commercially available software, an electronic source document created by any number of programs (e.g., word processors, spreadsheets, desktop publishing programs) can be converted to a PDF file, preserving the fonts, formatting, colors, and graphics of the source document, regardless of the application and platform used to create it. The PDF file can be copied onto a floppy disk or CD–ROM and shared with other users who may use PDF reading software to view, navigate through, and print the document exactly as it appears in its original form. Once we receive a PDF document, we can use our current software to compare the text of the file received with other PDF files and view, search, annotate, and print the file. Available software also allows us to copy text, tables, and figures from the file. Software to convert electronic files to PDF format is commercially available at a cost of approximately $100 to $300. Additionally, the technology necessary to create PDF documents is publicly available, and applicants that choose to do so may use their own software to create PDF documents for submission.

Although we believe that PDF is currently the best file format in which to submit labeling electronically, future advancements in computer technology and computer software design may result in new types of file formats and software to better meet our needs and those of industry. Therefore, we believe it is important to evaluate these new technologies as they become available. If we determine that a new technology provides important benefits over PDF, we need the flexibility to identify new or additional formats for electronic labeling submissions. For this reason, we are not proposing to require specifically that PDF be used to submit labeling content electronically. Rather, we are proposing that the content of labeling be submitted in a form that we can process, review, and archive. This language will provide us the flexibility to recommend file formats or software other than PDF in future guidance, to make electronic submissions easier.

C. Why Does the Agency Make Specific Recommendations for Electronic Labeling Submissions?

After the agency receives the labeling, we compare it to the last-submitted labeling and look for differences in text, figures, and other changes. In the process of review, we frequently copy, paste, and print portions of the labeling. These functions are most easily performed using PDF when: (1) There are no headers or footers (other than page numbers) to compare or copy; (2) there are no columns to interfere with the copy and paste function or with navigation through the labeling; (3) the font size is sufficiently large to be easily read; (4) the page orientation is portrait; (5) the pagination starts with page one to avoid confusion when referring to changes; and (6) the page size is not too large to be printed on a standard page and not too small to print efficiently. Therefore, electronic files submitted to us should be prepared, organized, and sent to us in accordance with the recommendations in the most recent agency guidance so that they may be easily reviewed and used. Submitting documents according to these recommendations will ensure a uniformity of submissions that will improve the efficiency and speed of agency reviews.

III. Description of the Proposed Rule

The proposal would revise our regulations to require electronic submission of the content of labeling for NDAs, certain BLAs, ANDAs, supplements, and annual reports. This requirement would be in addition to existing requirements, found elsewhere in our regulations, that copies of labeling be submitted. The proposal would also make minor changes to reformat and modernize certain regulatory provisions.

A. Electronic Submission of the Content of Labeling

Under the proposal, §§ 314.50(l), 314.81(b)(2)(iii), and 314.94(d)(1) would be revised to require applicants to submit the content of labeling in NDAs, ANDAs, supplements, and annual reports electronically in a form that we can process, review, and archive. Under proposed § 314.94(d)(1), ANDA applicants would be required to submit in electronic format the content of labeling for the proposed drug product (i.e., the content of the generic drug product labeling). ANDA applicants would not be required to submit in electronic format the content of labeling for the reference listed drug product. Under proposed § 601.14, applicants for biological products subject to the requirements of § 201.100(d)(3) would be required to submit the content of labeling in BLAs, supplements, and annual reports electronically in a form that we can process, review, and archive.

As discussed in section II of this document, the only type of electronic file format that we have the ability to

accept for processing, review, and archiving at this time is PDF, and the economic impact estimates in section IX of this document have been developed based on the assumption that PDF would be used. As new file formats and software applications are developed, we may recommend that different or additional types of file formats (i.e., other than PDF) should be used to submit labeling electronically. The language of the proposed rule (i.e., that the content of labeling must be submitted in a form that we can process, review, and archive) will provide us the flexibility to recommend file formats or software other than PDF in future guidance, if appropriate. If we later recommend other file formats or software, we intend to provide advance notice, in accordance with FDA's good guidance practice regulations under § 10.115 of this chapter, so that affected parties will have adequate time to convert to the new format or software. We will also identify any format or software changes in public docket number 92S–0251.[3] During the transition time, we intend to accept submissions using either file format or software.

B. Electronic and Paper Submission of Archival Copy of an NDA

Under current § 314.50(l)(1), applicants must submit the application form required under § 314.50(a) and samples and labeling information required under § 314.50(e) on paper, while other information required in the archival copy of an NDA (i.e., the information required under § 314.50(b), (c), (d), and (f)) may be submitted on microfiche or another suitable microform system. The proposal would revise § 314.50 (1)(1) to require applicants to submit the content of labeling electronically (i.e., in a computer file). (See section III.C of this document for proposal to delete specific references to microfiche or other suitable microform systems.)

Other portions of the archival copy of an NDA would be submitted to the agency either on paper or in electronic format provided that electronic submissions are made in accordance with part 11 of this chapter. Currently, under § 11.2(b)(2), FDA is able to accept all portions of the archival copy of the NDA electronically, except for documents requiring signatures. The agency is in the process of developing the ability to accept signatures electronically and plans to have this capability in the future. At that time, electronic signatures must comply with the requirements in part 11 pertaining to electronic signatures.

C. Deletion of References to Specific Media

The proposal would revise §§ 314.50(l)(1) and 314.94(d)(1) so that they no longer refer to means of submission through specific, nonpaper media. Section 314.50(l)(1) allows an NDA applicant to submit on microfiche the portions of the archival copy of an application described in § 314.50(b) through (d). If we agree, tabulations of patient data and case report forms described in § 314.50(f) may also be submitted on microfiche. If we agree, the applicant may use another suitable microform system. Section 314.94(d)(1) allows an ANDA applicant to submit an archival copy of the ANDA in any form, including microfiche, optical disc, and magnetic tape, if we find it acceptable.

We are proposing to delete the specific references to microfiche, microform, optical disc, and magnetic tape in §§ 314.50(l)(1) and 314.94(d)(1). We believe we can more readily respond to technological advances and our increasing knowledge of and experience with certain types of media by establishing regulations that set out general requirements for the use of media (i.e., on paper and in electronic format) and by using guidance documents to provide our current thinking on the specific types of media that we are able to process, review, and archive. We believe that this approach will allow us to be more responsive to the changing technological environment.

D. Formatting Changes

The proposal would amend § 314.50(l) by adding section headings to paragraphs (l)(1) through (l)(4) and by replacing the word ''shall'' with the word ''must.'' We anticipate that these minor changes will clarify the regulation and make it easier to read.

IV. Part 11 Requirements for Electronic Submissions

Our part 11 regulations, among other things, set forth the criteria under which records required to be submitted to us may be submitted in electronic format in lieu of paper. Section 11.2(b) states that, for records submitted to the agency, persons may use electronic records in lieu of paper records, in whole or part, provided the requirements of part 11 are met and the documents or parts of documents to be submitted have been identified by the agency in public docket No. 92S–0251[4] as being the type of submission the agency is prepared to accept in electronic format.

Part 11 permits the widest possible use of electronic technology, compatible with our responsibility to promote and protect the public health (62 FR 13430). Specifically, part 11 helps to ensure the integrity, authenticity, and when appropriate, the confidentiality of electronic records and helps to safeguard against the possible repudiation of those records. The controls in subpart B of part 11 are intended to further this purpose. However, with respect to the submission of labeling content in electronic format, the agency believes that several of the subpart B requirements are not necessary to further the goals of part 11. For example, validation for the system used to generate the labeling record under this proposal is not necessary. For the purposes of this rule, the applicant's verification that the information in the labeling record is accurate serves the same objective. The applicant also certifies on Form FDA 356h that the record is accurate. Because our review is based on the version of the labeling record submitted to us and earlier versions of the record or changes made to the earlier versions are not relevant to our analysis, other controls related to the creation, modification, and maintenance of the labeling records are also not needed. Therefore, we propose to exempt the submission of labeling content under this proposed rule from the requirements of § 11.10(a), (c) through (h), and (k) and the corresponding requirements imposed by § 11.30.

Labeling submitted in conjunction with NDAs, BLAs, and supplements to those applications has previously been identified by the agency in public docket No. 92S–0251 as being acceptable for submission in electronic format. Should this proposal be finalized, those portions of annual reports, ANDAs, and ANDA supplements to which the final rule is applicable will also be identified in the public docket as acceptable for submission in electronic format.

As discussed above, we found that some of the controls described in part 11 are not necessary to ensure the integrity and authenticity of labeling content submissions. Accordingly, we are reevaluating the necessity of some of the controls in part 11 as they apply to

[3]This docket can be accessed on the Internet at http://www.fda.gov/ohrms/dockets/dockets/92s0251/92s0251.htm.

[4]This docket can be accessed on the Internet at http://www.fda.gov/ohrms/dockets/dockets/92s0251/92s0251.htm.

different submissions, including records voluntarily submitted in electronic format. We may consider whether to propose amendments to the part 11 regulations as a result of our reevaluation. Sponsors should contact us with questions concerning the applicability of subpart B controls to records voluntarily submitted in electronic format.

V. Legal Authority

Our legal authority to amend our regulations governing the format of labeling for human prescription drugs and biologics derives from sections 201, 301, 501, 502, 503, 505, 506, 506A, 506B, 506C, 510, 513–516, 518–520, 701, 704, 721, and 801 of the act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 356a, 356b, 356c, 360, 360c–360f, 360h–360j, 371, 374, 379e, and 381); 15 U.S.C. 1451–1561; the Public Health Service Act (42 U.S.C. 216, 241, 262, 263, 264); and sec. 122, Public L. 105–115, 111 Stat. 2322 (21 U.S.C. 355 note).

VI. Paperwork Reduction Act of 1995

This proposed rule contains collections of information requirements that are subject to review by OMB under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). A description of these requirements are given below with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the date needed, and completing and reviewing each collection of information.

We invite comments on: (1) Whether the proposed collection of information is necessary for proper performance of our functions, including whether the information will have practical utility; (2) the accuracy of our 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: Requirements for Submission of Labeling for Human Prescription Drugs and Biologics in Electronic Format

Description: We are proposing to require that certain labeling content be submitted to us for review in electronic form. The proposal would require that the content of labeling for prescription drug and biological products that is required under § 201.100(d)(3) be submitted to us in electronic format. This labeling is submitted to us with NDAs, BLAs, ANDAs, supplements, and annual reports. We are proposing to require that the content of this labeling be submitted in electronic format because the use of computer technology to identify changes in different versions of the labeling would greatly enhance the accuracy and speed of our review of product labeling. The ability to quickly identify changes in labeling text would also shorten the time needed to approve labeling changes.

As discussed in section I of this document, copies of product labeling are currently required to be submitted to us for review in NDAs, certain BLAs, ANDAs, certain supplements, and annual reports under §§ 314.50, 314.70, 314.81, 314.94, 314.97, 314.98, 601.2, and 601.12. Under this proposed rule, copies of labeling may be submitted electronically or on paper. The proposal would require that the content of the labeling required under § 201.100(d)(3) be submitted in electronic format.

The proposal would amend current §§ 314.50(l), 314.81(b)(2)(iii), 314.94(d)(1), and part 601 to require that the content of labeling (i.e., labeling required under § 201.100(d)(3), including all text, tables, and figures) be submitted to us electronically in a form that we can process, review, and archive. Under § 314.71, supplements to NDAs and ANDAs submitted to us under §§ 314.70 and 314.97 must follow the procedures of § 314.50. In addition, ANDA annual reports submitted to us under § 314.98 must follow the requirements of § 314.81. Under proposed § 601.14, the content of labeling submitted with BLAs under § 601.2, supplements to BLAs under § 601.12, and BLA annual reports under § 601.12 for products subject to the requirements of § 201.100(d)(3) must be in electronic format. Therefore, if labeling is required as part of an NDA, ANDA, or BLA, an NDA, ANDA, or BLA supplement, or an NDA, ANDA, or BLA annual report, the content of labeling must be submitted to us electronically in a form that we can process, review, and archive. As discussed in section II of this document, these electronic files should be provided to us in accordance with the recommendations in agency guidance.

Description of Respondents: An applicant submitting an NDA, ANDA, BLA, supplement, or annual report to us for a drug or biological product.

Burden Estimate: Table 1 of this document provides an estimate of the annual reporting burden under the proposed rule.

This rule would require applicants to submit in an electronic form that we can process, review, and archive, the content of labeling with NDAs, BLAs, ANDAs, annual reports, and certain supplements.[5] Currently, applicants are not required to submit this labeling electronically. Because we do not know the number of applicants that currently have the capability to submit electronic files and do not have firsthand information on how labeling files are currently maintained, the following estimates are based on our experience with voluntary electronic submissions and with converting word processing files to PDF format. Therefore, we request that interested parties submit comments on the accuracy of these estimates.

The reporting burdens for submitting labeling as currently required under §§ 314.50, 314.70, 314.81, 314.94, 314.97, and 314.98 have previously been estimated by us, and this collection of information was approved by OMB until March 31, 2002, under OMB control number 0910–0001. The reporting burdens associated with current §§ 601.2 and 601.12 have also previously been estimated, and this collection of information was approved by OMB until March 31, 2003, under OMB control number 0910–0338, and until August 31, 2003, under OMB control number 0910–0315, respectively. We are not reestimating these approved burdens in this rulemaking. Only the additional reporting burdens associated with the electronic submission of the content of labeling are estimated.

New NDAs (§ 314.50), ANDAs (§ 314.94), and BLAs (§ 601.2): Based on data in the approved collections of information for §§ 314.50, 314.94, and 601.2, we estimate that approximately 83 NDA applicants, 117 ANDA applicants, and 17 BLA applicants (respondents) submit applications to us annually. We estimate that the total annual responses, i.e., the total number of NDAs, ANDAs, and BLAs submitted to us per year, will remain approximately 124 NDAs, 464 ANDAs, and 63 BLAs. Based on our experience with voluntary electronic submissions and our knowledge of the drug and biologic industries, we assume that applicants for new NDAs, ANDAs, and BLAs will already have the necessary labeling in an electronic format that can be easily accessed and converted to a PDF file. Thus, we have estimated that the hours per response, i.e., the

[5] As discussed in section II of this document, PDF is the only type of electronic file format that we have the ability to accept for processing, reviewing, and archiving at this time. Therefore, the estimates in this section are based on submission of files in PDF format.

additional time necessary for submission of the content of labeling in electronic format for these applications, will be less than 15 minutes. Therefore, we estimate that respondents will spend approximately 163 hours per year submitting the content of labeling to us in accordance with the proposed rule.

Supplements to NDAs (§ 314.70) and ANDAs (§ 314.97) and BLAs (§ 601.12(f)(1) and (f)(2)): Based on data in the approved collections of information for §§ 314.70, 314.97, and 601.12(f)(1) and (f)(2), we estimate that approximately 418 NDA applicants, 152 ANDA applicants, and 22 BLA applicants (respondents) submit supplements to approved applications to us annually. We estimate that the total annual responses, i.e., the total number of NDA, ANDA, and BLA supplements submitted to us per year, will remain approximately 2,229 NDA supplements, 3,000 ANDA supplements, and 22 BLA supplements. Based on our experience reviewing supplements to applications and because not all NDA and ANDA supplements are required to include labeling, we estimate that, under the proposed rule, approximately 45 percent of NDA supplements (i.e., 1,003 NDA supplements) and 20 percent of ANDA supplements (i.e., 600 ANDA supplements) would be required to include the content of labeling in electronic form. Under the proposed rule, all 22 BLA labeling supplements would be required to include the content of labeling in electronic form. Based on our experience with voluntary electronic submissions and our knowledge of the drug and biologic industries, we assume that applicants submitting supplements to NDAs, ANDAs, and BLAs will already have the necessary labeling in an electronic format that can be easily accessed and converted to a PDF file. Thus, we have estimated that the hours per response, i.e., the additional time necessary for submission of the content of labeling in electronic format for these supplements, will be less than 15 minutes. Therefore, we estimate that respondents would spend approximately 406 hours per year submitting the content of labeling to us in supplements under the proposed rule.

Annual Reports for NDAs (§ 314.81), ANDAs (§ 314.98), and BLAs (§ 601.12(f)(3)): Based on data in the approved collections of information for §§ 314.81, 314.98, and 601.12(f)(3), we estimate that approximately 269 NDA applicants, 265 ANDA applicants, and 70 BLA applicants (respondents) submit annual reports to us annually. We also estimate that each NDA applicant submits to us approximately 9.06 annual reports, each ANDA applicant submits approximately 17.17 annual reports, and each BLA applicant submits approximately 1.42 annual reports each year. Further, we estimate that the total annual responses, i.e., the total number of annual reports submitted to us per year, will remain approximately 2,438 NDA annual reports, 4,551 ANDA annual reports, and 100 BLA annual reports.

Based on our experience with voluntary electronic submissions and our knowledge of the drug and biologic industries, we estimate that approximately 80 percent of NDA annual reports (1,950 NDA annual reports), 70 percent of ANDA annual reports (3,186 ANDA annual reports), and 80 percent of BLA annual reports (80 BLA annual reports), will already have the necessary labeling in an electronic format that can be easily accessed and converted to a PDF file. As discussed above, we estimate that each NDA applicant submits to us approximately 9.06 annual reports, each ANDA applicant submits approximately 17.17 annual reports, and each BLA applicant submits approximately 1.42 annual reports each year. Therefore, approximately 215 NDA applicants, 186 ANDA applicants, and 56 BLA applicants can easily access labeling in electronic form and convert it to a PDF file. For the applicants submitting these annual reports, we estimate that the hours per response, i.e., the additional time necessary for submission of the content of labeling in electronic format in the annual report, will be less than 15 minutes.

We recognize that annual reports for some drug and biological products, particularly older products for which labeling changes have not been made in several years, may require additional steps. To include labeling content in electronic format, we estimate that approximately 20 percent of NDA annual reports (488 NDA annual reports), 30 percent of ANDA annual reports (1,365 ANDA annual reports), and 20 percent of BLA annual reports (20 BLA annual reports) will be submitted by applicants who may need to access the labeling in their archives and put the content of labeling into an electronic format and convert it to a PDF file. As discussed above, we estimate that each NDA applicant submits to us approximately 9.06 annual reports, each ANDA applicant submits approximately 17.17 annual reports, and each BLA applicant submits approximately 1.42 annual reports each year. Therefore, under the proposed rule, approximately 54 NDA applicants, 79 ANDA applicants, and 14 BLA applicants would need to put labeling content in an electronic format and convert it to a PDF file. We estimate that the hours per response, i.e., the time it will take an applicant to submit the labeling content electronically for these annual reports, will be approximately 8 hours.

Therefore, we estimate that in the first year, respondents will spend approximately 16,289 hours submitting the content of labeling to us in annual reports under the proposed rule. This expenditure of time will only be necessary the first time that an annual report is submitted with the content of labeling in electronic format. Once the content of labeling has been converted to an electronic format, the time necessary to submit the content of labeling in subsequent annual reports will be the same as that for the other types of submissions, or less than 15 minutes. Therefore, we estimate that, in subsequent years, respondents will spend approximately 1,773 hours per year submitting the content of labeling in annual reports.

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
Applications:					
3.14.50	83	1.49	124	.25	31
314.94	117	3.96	464	.25	116
601.14 (Applications submitted under § 601.2)	17	3.71	63	.25	16
Subtotal, applications					163
Supplements:					
314.70	418	2.39	1,003	.25	251

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]—Continued

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
314.97	152	3.94	600	.25	150
601.14 (Supplements submitted under § 601.12(f)(1) and (f)(2))	22	1.0	22	.25	6
Subtotal, supplements					407
Annual Reports:					
314.81 (Products not requiring additional steps for electronic submission)	215	9.06	1,950	.25	488
314.81 (Products requiring additional steps for electronic submission)	54	9.06	488	8	3,904
314.98 (Products not requiring additional steps for electronic submission)	186	17.17	3,186	.25	797
314.98 (Products requiring additional steps for electronic submission)	79	17.17	1,365	8	10,920
601.14 (Annual reports submitted under § 601.12(f)(3) not requiring additional steps for electronic submission)	56	1.4	80	.25	20
601.14 (Annual reports submitted under § 601.12(f)(3) requiring additional steps for electronic submission)	14	1.4	20	8	160
Subtotal, annual reports, year one					16,289
Subtotal, annual reports, subsequent years[2]					1,773
Total, year one					16,859
Total, subsequent years[2]					2,343

[1] There are one-time capital costs to: (1) Acquire computer software; (2) train employees to use the software; and (3) convert certain labeling to an electronic format. These costs are estimated to be about $934,650 (see section IX of this document). There are no operating or maintenance costs associated with this collection of information.

[2] We estimate that for certain annual reports, respondents will spend 8 hours per response in the first year. We estimate that in subsequent years respondents will spend less than 15 minutes per response for all annual reports.

In compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d)), we have submitted the information collection requirements of this proposed rule to OMB for review. Interested persons are requested to send comments regarding information collection by June 3, 2002, to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington DC 20503, Attn: Stuart Shapiro, Desk Officer for FDA.

VII. Environmental Impact

We have determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that the proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we have concluded that the proposed rule does not contain policies that have federalism implications as defined in the order and, consequently, a federalism summary impact statement is not required.

IX. Analysis of Economic Impacts

We have examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612 (as amended by subtitle D of the Small Business Regulatory Fairness Act of 1996 (Public Law 104–121))), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). 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). Under the Regulatory Flexibility Act, if a rule may have a significant economic impact on a substantial number of small entities, an agency must consider alternatives that would minimize the economic impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written assessment of anticipated costs and benefits before proposing any rule that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million in any one year (adjusted annually for inflation).

We believe that this proposed rule is consistent with the regulatory philosophy and principles identified in Executive Order 12866 and in these two statutes. The proposed rule is a significant regulatory action as defined in section 3 paragraph (f)(4) of the Executive order. However, as shown below, the proposed rule will not be an economically significant regulatory action as defined by the Executive order and will not require further analysis under the Regulatory Flexibility Act.

The Unfunded Mandates Reform Act of 1995 does not require FDA to prepare a statement of costs and benefits for the proposed rule because the proposed rule would not result in an expenditure of $100 million in any one year, adjusted for inflation. The current inflation-adjusted statutory threshold is approximately $110 million.

The purpose of this proposal is to require applicants to submit in electronic format the content of labeling required under § 201.100(d)(3) in NDAs, ANDAs, BLAs, annual reports, and applicable supplements. Submissions in electronic format will help simplify and speed up our review of these documents. Currently, applicants may voluntarily submit such data in electronic form, but they are not required to do so. The rule will require all applicants with approved and new NDAs, BLAs, and ANDAs to convert the

content of labeling to an electronic format for submission. At this time, the type of electronic file format that we have the ability to accept for processing, reviewing, and archiving is PDF. Applicants that do not already have the capabilities to create PDF files will have to acquire the software and expertise to do so or make contractual arrangements to have documents converted.

The economic burden on industry will include a one-time cost to acquire the appropriate computer software and train employees on its use. Applicants may also incur additional one-time costs to revise applications that have not had any labeling changes within the last few years to a format that can be converted to a PDF file. We do not know the number of applicants that currently have the capability to submit electronic files, nor do we have firsthand information on how labeling files are currently maintained or on how much time will be required to train employees on the software and new procedures. The following estimates, therefore, are based on agency experience with voluntary electronic submissions and with converting word processing files to PDF format. We request that interested parties submit comments on the accuracy of these estimates.

We receive annually approximately 651 applications, 7,089 annual reports, and 1,625 supplements that contain labeling from approximately 610 applicants. Based on our experience working with voluntary electronic submissions, we estimate that overall approximately 70 percent of the applicants (427) already have the necessary software and trained personnel to comply with the proposed rule. The remaining 30 percent of applicants (183) would need to purchase software, which costs about $250. Based on agency review, approximately 78 percent of these 183 applicants (143) would be considered small (fewer than 750 employees for drug product manufacturers, fewer than 500 employees for biological product manufacturers). We estimate that each small applicant would need to purchase only one copy of the software, for a total of (143) copies. The remaining 22 percent of applicants (40) that would need to purchase software are large entities. The agency estimates that each of these firms would need to purchase about 3 copies of the software, or 120 copies (40 x 3). Thus, the total one-time cost for software is $65,750 ((143 + 120) x $250). Training costs include the cost of the software training course (estimated at $150 for a 6-hour course) and the wages of the employees attending the course (assuming an average weighted wage rate of $40 per hour). We estimate that applicants would train two employees per software purchase (526 employees), for a total one-time cost of $205,140 ([($150 + (6 hours x $40)) x 526]). The total one-time cost for software and training combined is estimated to be $270,890 ($65,750 + $205,140).

The cost to convert the applicable labeling to an electronic format is a one-time cost. The cost of conversions for new NDAs, BLAs, and ANDAs will be nominal because the file would be in a format easily convertible to PDF. We receive annually approximately 1,625 supplements that would be subject to the proposed rule. As the majority of products for which supplements are submitted would have had labeling changes within the last few years, most labeling files would be easily accessible and require an estimated 15 minutes to process. Thus, the total number of hours needed to convert applicable labeling in supplements to a PDF file format is 406. Labeling in all 7,089 annual reports would also need to be converted. The conversion of this labeling to a PDF file for about 20 percent of NDA annual reports (488), 30 percent of ANDA annual reports (1,365), and 20 percent of BLA annual reports (20) would require additional time to complete because they are not in a format easily convertible to PDF. We estimate that these annual reports would require 8 hours to complete, for a total of 14,984 hours ((488 + 1,365 + 20) x 8). The remaining annual reports (5,216) would require 15 minutes, for a total of 1,304 hours. Thus, the total number of hours needed to convert applicable labeling to a PDF file format in annual reports is 16,188 (14,984 + 1,304). Using the weighted average wage rate ($40 per hour), the total one-time costs to convert applicable labeling in supplements and annual reports would be $663,760 ((406 + 16,188) x $40). The cost for the entire rule is estimated to be about $934,650 ($270,890 + $663,760).

Approximately 300 domestic entities would be affected by this proposed rule, about 240 of which meet the Small Business Administration's definition of a small entity (fewer than 750 employees for drug product manufacturers, fewer than 500 employees for biological product manufacturers). The economic impact of this proposed rule would vary by firm depending on the number of applications they hold and whether or not the company has PDF capabilities. The number of applications per firm ranges from 1 to 124, with a median of 4 applications per small entity. The average small entity has about seven applications, and, assuming each needed to purchase the software and train employees, this rule would cost the firm less than $1,000, or about $140 per application. Because these costs would almost certainly be less than 1 percent of product revenues, the agency certifies that this proposed rule will not, if finalized, have a significant economic impact on a substantial number of small entities.

X. Proposed Effective Date

FDA proposes that any final rule that may issue regarding this proposal become effective 180 days after its date of publication in the **Federal Register**.

XI. Request for Comments

Interested persons may submit to the Dockets Management Branch (address above) written or electronic comments regarding this proposal by August 1, 2002. 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 Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

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 parts 314 and 601 be amended as follows:

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

1. The authority citation for 21 CFR part 314 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 356a, 356b, 356c, 371, 374, 379e.

2. Section 314.50 is amended by revising paragraph (l)(1); by adding headings for paragraphs (l)(2), (l)(3), and (l)(4); by removing from paragraphs (l)(2) and (l)(3) the word ''shall'' and adding in its place the word ''must''; and by adding paragraph (l)(5) to read as follows:

§ 314.50 Content and format of an application.

* * * * *

(l) *Format of an original application.* (1) *Archival copy.* The applicant must submit a complete archival copy of the application that contains the information required under paragraphs (a) through (f) of this section. FDA will maintain the archival copy during the review of the application to permit individual reviewers to refer to information that is not contained in their particular technical sections of the application, to give other agency personnel access to the application for official business, and to maintain in one place a complete copy of the application. Except as required by paragraph (1)(1)(i) of this section, applicants may submit the archival copy on paper or in electronic format provided that electronic submissions are made in accordance with part 11 of this chapter.

(i) *Labeling.* The content of labeling required under § 201.100(d)(3) of this chapter (commonly referred to as the package insert or professional labeling), including all text, tables, and figures, must be submitted to the agency in electronic format as described in paragraph (l)(5) of this section. This requirement is in addition to the requirements of paragraph (e)(2)(ii) of this section that copies of the formatted label and all labeling be submitted. Submissions under this paragraph must be made in accordance with part 11 of this chapter, except for the requirements of § 11.10(a), (c) through (h), and (k), and the corresponding requirements of § 11.30.

(ii) [Reserved]

(2) *Review copy.* * * *

(3) *Field copy.* * * *

(4) *Binding folders.* * * *

(5) *Electronic format submissions.* Electronic format submissions must be in a form that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files).

3. Section 314.81 is amended by revising paragraph (b)(2)(iii) to read as follows:

§ 314.81 Other postmarketing reports.

* * * * *

(b) * * *

(2) * * *

(iii) *Labeling. (a)* Currently used professional labeling, patient brochures or package inserts (if any), and a representative sample of the package labels.

(b) The content of labeling required under § 201.100(d)(3) of this chapter (i.e., the package insert or professional labeling), including all text, tables, and figures, must be submitted in electronic format. Electronic format submissions must be in a form that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files). Submissions under this paragraph must be made in accordance with part 11 of this chapter, except for the requirements of § 11.10(a), (c) through (h), and (k), and the corresponding requirements of § 11.30.

(c) A summary of any changes in labeling that have been made since the last report listed by date in the order in which they were implemented, or if no changes, a statement of that fact.

* * * * *

4. Section 314.94 is amended by revising paragraph (d)(1) to read as follows:

§ 314.94 Content and format of an abbreviated application.

* * * * *

(d) * * * (1) The applicant must submit a complete archival copy of the abbreviated application as required under paragraphs (a) and (c) of this section. FDA will maintain the archival copy during the review of the application to permit individual reviewers to refer to information that is not contained in their particular technical sections of the application, to give other agency personnel access to the application for official business, and to maintain in one place a complete copy of the application.

(i) *Format of submission.* An applicant may submit portions of the archival copy of the abbreviated application in any form that the applicant and FDA agree is acceptable, except as provided in paragraph (d)(1)(ii) of this section.

(ii) *Labeling.* The content of labeling required under § 201.100(d)(3) of this chapter (commonly referred to as the package insert or professional labeling), including all text, tables, and figures, must be submitted to the agency in electronic format as described in paragraph (d)(1)(iii) of this section. This requirement applies to the content of labeling for the proposed drug product only and is in addition to the requirements of paragraph (a)(8)(ii) of this section that copies of the formatted label and all proposed labeling be submitted. Submissions under this paragraph must be made in accordance with part 11 of this chapter, except for the requirements of § 11.10(a), (c) through (h), and (k), and the corresponding requirements of § 11.30.

(iii) *Electronic format submissions.* Electronic format submissions must be in a form that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files).

* * * * *

PART 601—LICENSING

5. The authority citation for 21 CFR part 601 continues to read as follows:

Authority: 15 U.S.C. 1451–1561; 21 U.S.C. 321, 351, 352, 353, 355, 356b, 360, 360c–360f, 360h–360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263, 264; sec. 122, Pub. L. 105–115, 111 Stat. 2322 (21 U.S.C. 355 note).

6. Add 601.14 to subpart C to read as follows:

§ 601.14 Regulatory submissions in electronic format.

(a) *General.* Electronic format submissions must be in a form that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files.)

(b) *Labeling.* The content of labeling required under § 201.100(d)(3) of this chapter (commonly referred to as the package insert or professional labeling), including all text, tables, and figures, must be submitted to the agency in electronic format as described in paragraph (a) of this section. This requirement is in addition to the provisions of §§ 601.2(a) and 601.12(f) that require applicants to submit specimens of the labels, enclosures, and containers, or to submit other final printed labeling. Submissions under this paragraph must be made in accordance with part 11 of this chapter except for the requirements of § 11.10(a), (c) through (h), and (k), and the corresponding requirements of § 11.30.

Dated: April 26, 2002.

Lester M. Crawford,

Deputy Commissioner.

Tommy G. Thompson,

Secretary of Health and Human Services.

[FR Doc. 02–11039 Filed 5–1–02; 8:45 am]

BILLING CODE 4160–01–S