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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 314 and 601

[Docket No. 2000N–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: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending 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 final rule requires 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 will simplify the drug labeling review process and speed up the approval of labeling changes.

DATES: The rule is effective [*insert date 180 days after publication in the* **Federal Register**].

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SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of May 3, 2002 (67 FR 22367), FDA published a proposed rule to require the submission of the content of labeling for human prescription drugs and certain biologics in electronic format in a form that FDA can process, review, and archive. This electronic submission requirement would necessitate the amendment of FDA's regulations under §§ 314.50(l) (21 CFR 314.50(l)), 314.81(b)(2)(iii) (21 CFR 314.81(b)(2)(iii)), 314.94(d)(1) (21 CFR 314.94(d)(1)), and the addition of § 601.14 (21 CFR 601.14).

Under current regulations, as noted in the preamble to the proposed rule, labeling for the archival copy of an NDA must be submitted to the agency on paper, labeling for the archival copy of an ANDA may be submitted in any form that FDA and the applicant agree upon, and the current regulations for BLA labeling do not specify a format for submission to the agency. 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

[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.

201.100(d)(3)), commonly referred to as the "package insert" or "professional labeling")[2] and other labeling. This final rule applies to the electronic submission of the content of labeling, defined as the contents of the package insert or professional labeling, including all text, tables, and figures.

Each year FDA conducts a word-for-word comparison of the labeling as part of the review process for 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.[3] Because reviewers currently conduct these comparisons manually using two paper copies of the labeling, the process is slow and subject to error. Requiring the electronic submission of labeling for NDAs, certain BLAs, ANDAs, supplements, and annual reports will greatly enhance the accuracy and speed of labeling review. This will result in increased protection of the public health because electronic review and comparison of labeling files will provide a higher degree of certainty that all sections of prescription drug labeling are correct.

Although FDA has not previously required regulatory submissions in electronic format, we have issued several guidances describing how to make voluntary electronic submissions to the agency. In the **Federal Register** of January 28, 1999 (64 FR 4433), we (FDA) issued a guidance on general considerations for electronic submissions entitled "Providing Regulatory Submissions in Electronic Format—General Considerations" (general considerations guidance). In the general considerations guidance, we included

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[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.

[3] We also 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)(iv).

a description of the types of electronic file formats that we are able to accept for processing, reviewing, and archiving electronic documents. 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—NDAs," which provided information on how to submit a complete archival copy of an NDA in electronic format. 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). Most recently, we published a guidance for ANDAs entitled "Providing Regulatory Submission in Electronic Format—ANDAs" (67 FR 43331, June 27, 2002). In addition, part 11 (21 CFR part 11), concerning electronic records and electronic signatures, describes certain controls for electronic regulatory submissions and states that we are prepared to accept those regulatory submissions that have been identified in the public docket (62 FR 13430, March 20, 1997).

FDA received 13 comments (which raised 21 issues) on the proposed rule and addresses each of those comments in section III of this document. The majority of the comments supported the proposed amendments to FDA's regulations. After careful consideration of the comments, the agency is adopting this final rule without any changes from the proposed rule. The final rule is described in section II of this document.

II. Description of the Final Rule

We are revising our regulations to require the electronic submission of the content of labeling (i.e., the content of the package insert or professional labeling, including all text, tables, and figures) for NDAs, certain BLAs,

ANDAs, supplements, and annual reports. This requirement is in addition to existing requirements, found elsewhere in our regulations, that copies of the label and labeling and specimens of enclosures be submitted.

Under the amended regulations that we are adopting in this final rule, §§ 314.50(l), 314.81(b)(2)(iii), and 314.94(d)(1) are 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.[4] Under new § 314.94(d)(1), ANDA applicants are 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). As previously stated in the preamble to the proposed rule, ANDA applicants are not required to submit in electronic format the content of labeling for the reference listed drug product. Section 601.14 is added to require applicants for biological products subject to the requirements of § 201.100(d)(3) to submit the content of labeling in BLAs, supplements, and annual reports electronically in a form that we can process, review, and archive.[5]

At this time, portable document format (PDF) is the only type of electronic file format that we have the ability to accept for processing, reviewing, and archiving. PDF is commonly used, easily obtainable, and affordable. Software to convert electronic files to PDF is commercially available at a cost of

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[4] The submission of labeling for the archival copy of an NDA is required under § 314.50(e)(2)(ii). Section 314.71(b) (21 CFR 314.71(b)) requires that supplements to approved applications submitted to the agency under § 314.70 (21 CFR 314.70) follow the procedures described in § 314.50. Section 314.81(b)(2)(iii) (21 CFR 314.81(b)(2)(iii)) requires that annual reports include "currently used professional labeling, patient brochures, or package inserts." With respect to the archival copy of an ANDA, § 314.94(a)(8)(ii) requires copies of the label and all labeling for the drug product. 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. Under § 314.98(c) (21 CFR 314.98(c)), annual reports for ANDAs must be submitted as required in § 314.81(b)(2)(iii).

[5] 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.

approximately $100 to $300. The technology necessary to create PDF documents is also publicly available. Because PDF is the only acceptable file type, references to specific media (microfiche, microform, optical disc, and magnetic tape) under §§ 314.50(l)(1) and 314.94.(d)(1) will be deleted.

To be responsive to technological advances, we may recommend in the future that new file formats and software applications be used to submit labeling electronically. As mentioned in the preamble to the proposed rule, we will provide advance notice, in accordance with FDA's good guidance practice regulations under § 10.115 (21 CFR 10.115), so that affected parties will have adequate time to convert to any new format or software. In addition, we expect that such format or software will be widely available before we switch to a new technology. Changes in format and/or software will be identified in public docket number 92S–0251. During any such transition, we will accept submissions using either file format or software.

Finally, these new regulations also make minor changes to reformat and modernize certain regulatory provisions. This final rule is amending § 314.50(l) by adding headings to paragraphs (l)(1) through (l)(4) and by removing the word "shall" and adding in its place the word "must."

III. Comments on the Proposed Rule

FDA received 13 sets of written comments on the proposed rule from manufacturers, trade associations, advocacy groups, consulting firms, and individuals. The majority of the comments supported FDA's proposal to require that the content of certain labeling be submitted electronically in a form that FDA can process, review, and archive. A few comments requested clarification on various aspects of the rule and one comment opposed the

exemptions from specific controls under part 11. A summary of the comments received and the agency's responses follows:

A. General Comments

(Comment 1) One comment identified as a typographical error the citation of § 314.50(l). The comment suggested that § 314.50(l)(1)(i) was being referenced as (1)(1)(i).

(Response) This is not a typographical error; we are citing to § 314.50(l)(1)(i) in the proposed rule, but the lower case letter L ("l") looks similar to the number 1.

(Comment 2) One comment recommended adding changes to § 314.70 and § 601.12 to address labeling supplements.

(Response) FDA believes that § 314.70 and § 601.12 do not need any changes because the recommended requirements already exist.

Under § 314.71, all procedures that apply to an application under § 314.50 also apply to supplement submissions. Thus, by amending the provisions in § 314.50, the final rule also covers the requirements for labeling supplements. Similarly, § 601.14 requires applicants for biological products subject to the requirements of § 201.100(d)(3) to submit the content of labeling in BLAs, supplements, and annual reports electronically in a form that FDA can process, review, and archive.

(Comment 3) One comment stated that it supported the adoption of regulations to require bar coding for all pharmaceuticals.

(Response) The agency is pursuing bar coding initiatives separately from this rulemaking. A proposed rule to require bar codes on certain human drug product labels and biological product labels was published in the **Federal Register** of March 14, 2003 (68 FR 12500). This final rule deals solely with

the content of labeling for human prescription drugs and biologics submitted to FDA in electronic format that FDA can process, review, and archive.

(Comment 4) Although supportive of the proposed rule, one comment was concerned about industry initiatives to use this rule to advocate for electronic versions as a substitute for printed patient inserts (PPIs).[6] The comment expressed concern that this rule could serve as a basis for the elimination of printed PPIs.

(Response) FDA understands the comment's concern, but the agency's regulation of PPIs is unrelated to the requirement to submit the content of labeling electronically. This rule requires that the content of labeling (i.e., the content of the package insert or professional labeling, including all text, tables, and figures) be submitted electronically. It does not alter the current regulatory treatment of PPIs. The PPIs can be submitted in paper or electronic format under part 11. If the PPI is submitted electronically, it must appear in the electronic format as it would in printed form.

(Comment 5) One comment mentioned that this rule will enable the agency to move forward with other initiatives to make labeling more rapidly available. The comment asks the agency to consider providing certain recommendations on a standard database for labeling and standard display formats for viewing labels.

(Response) FDA welcomes the comment, and we are working on several initiatives to make labeling more readily available to the public. This rule is a necessary step to provide FDA with the information needed to improve the readability, organization, and access to labeling information, including the possibility of using the information in a standard database.

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[6] The comment refers to patient package inserts as "PIs." FDA, though, refers to such inserts as "PPIs.".

B. Applicability/Scope of the Proposed Rule

(Comment 6) One comment requested that FDA clarify whether the Circular of Information for the Use of Human Blood Components (the Circular) is exempt from this rule. The comment stated that the Circular is prepared on a biannual basis by a committee representing all blood organizations and a single submission is made to FDA. The same version of the Circular is used by the majority of licensed blood establishments.

(Response) It is true that FDA reviews a version of the Circular that a consortium of blood establishments submits periodically. Although individual blood establishments may use different versions of the Circular and must submit those versions in supplemental applications to FDA, the amount of variation from the FDA-recognized Circular is so minimal that electronic submission is not necessary at this time. Therefore, the final rule does not require the submission of the Circular to the agency in electronic format.

(Comment 7) Several comments asked for clarification of the following statement in the proposed rule: "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." The comments requested that the agency explicitly state that no paper copies of labeling are to be submitted.

(Response) The content of labeling is a new labeling type not previously required in the regulations to be submitted. The content of labeling, defined as the contents of the package insert or professional labeling, including all text, tables, and figures for prescription products approved under an ANDA, BLA, or NDA, does not replace any previously required labeling type, including the package insert. In other words, the regulations require the package insert to

be submitted in addition to the content of labeling. However, no paper copies of any labeling are required. As discussed in our response to comment 4, the applicant has the option of providing the package insert in paper or electronic format under part 11. The package insert, if submitted electronically, must appear as it would in printed form. Submission in this form allows us to evaluate the format of the package insert, such as font size and positioning of the text.

(Comment 8) A few comments asked for clarification of whether the rule requires the submission in electronic format of all types of labeling, such as carton and container labels, labels submitted with advertising material, and labeling that might be submitted with periodic adverse drug experience reports.

(Response) The agency did not intend that the final rule require the electronic submission of the previously mentioned types of labeling. The rule requires only that the content of labeling (i.e. the content of the package insert or professional labeling, including all text, tables, and figures) be submitted in electronic format.

(Comment 9) Some comments requested clarification of whether the rule restricts the submission of labeling in electronic format to the content of labeling.

(Response) The agency did not intend to restrict the voluntary submission of labeling in electronic format. Under part 11, an applicant may submit labeling in electronic format as long as the controls in part 11 are met and the labeling is listed in public docket number 92S–0251.[7] Because the agency

[7] A recent draft guidance issued by the agency provides for the exercise of enforcement discretion with respect to the following part 11 requirements: Validation (§ 11.10(a) (21 CFR 11.10(a))); copies of records § 11.10(b)); record retention (§ 11.10(c)); audit trails (§ 11.10(e) and (k)(2)); and any corresponding requirements in § 11.30. See FDA guidance for industry

has listed labeling in conjunction with NDAs, BLAs, and ANDAs in public docket number 92S–0251, applicants may submit all labeling for an NDA, BLA, or ANDA in electronic format.

(Comment 10) Two comments suggested that the electronic submission of labeling submitted with annual reports under § 314.81 should be optional if the product's labeling has not been revised beyond editorial changes. The comments noted that the labeling revisions to older products are infrequent and often insubstantial in nature; therefore, the submission of annual report labeling is not justified by the objectives of this rule.

(Response) FDA disagrees that the electronic submission of labeling in the annual report is not justified by the objectives of the final rule. The labeling submitted with the annual report, aside from editorial corrections, can also include other changes related to the manufacturing of the product. As with other labeling changes, these changes must be reviewed and require the same degree of comparison with previous versions of labeling. In addition, the labeling changes described in the annual report must be included in FDA's database. Finally, it is important to note that in our economic analysis, we found that the one-time costs to convert the labeling in annual reports to electronic format would not be overly burdensome (see section VIII of this document). Accordingly, the electronic submission of labeling submitted with annual reports under § 314.81 is not optional.

C. Reviewer Support and Training

(Comment 11) Some comments expressed concern that reviewers will accept "special requests" to receive the labeling in paper format or other formats to bypass existing agency guidance on electronic submissions. These

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entitled "Part 11, Electronic Records; Electronic Signatures—Scope and Application," available at *www.fda.gov/cder/guidance*.

same comments emphasized the importance of training and support of reviewers and staff in the use of electronic review and version comparison utilities.

(Response) FDA agrees that reviewers should not "bypass" our guidance documents. We train reviewers and managers on the details and provisions of guidance documents. When there are differences in opinion concerning the meaning of such provisions, it is best for the applicant and agency personnel to discuss those differences to ensure that everyone understands the relevant issues and the parties' respective positions. In addition, we will update our specific policy and procedure documents for reviewers to help enforce the common practice of reviewing documents electronically. The reviewers and staff will have sufficient training and support to fulfill their duties in reviewing the electronic version of the content of labeling.

(Comment 12) One comment pointed out that the Office of Generic Drugs (OGD) has limited experience with electronic labeling because it has only recently published guidance on providing an ANDA in electronic format.[8] The comment recommended that OGD pilot a program with industry to accept and process electronic labeling before the effective date of this rule.

(Response) FDA does not believe a pilot program is necessary to prepare OGD reviewers for the implementation of this rule. OGD reviewers used the electronic label review technology for many years before the issuance of the guidance on electronic submissions of ANDAs[9] and; therefore, have adequate experience in this area.

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[8] See "Providing Regulatory Submission in Electronic Format—ANDAs" guidance (67 FR 43331, June 27, 2002).

[9] Id.

D. Requiring Electronic Submission

(Comment 13) The comments were overwhelmingly supportive of requiring the electronic submission of the content of labeling. The comments commend FDA's goal of using electronic labeling to facilitate labeling reviews. However, a few comments suggested that the agency use appropriate metrics for tracking the gains associated with the electronic submission of labeling.

(Response) The agency agrees with the comment, and notes that, as explained in section II.A of the proposed rule, there will be numerous benefits from the regulation, particularly through enhancing the accuracy and speed of the labeling review process. Nevertheless, it may be difficult to quantify precisely the improvements derived solely from receiving labeling in electronic format because we also plan to improve our current business practice for processing and reviewing such labeling changes. To the extent possible, we plan to evaluate the success of all these changes and hope to make the results of our evaluations available to the public.

(Comment 14) A few comments suggested that the implementation of the rule would improve the availability of labeling to the public.

(Response) We believe that a number of changes are needed to improve the public's access to medication information. This rule is an important and necessary step toward that goal, because it will greatly enhance the accuracy and speed of labeling reviews. We are actively working with the pharmaceutical industry, other government agencies, and health care information suppliers to achieve success in this area. For example, we are currently working with several agencies, including the National Library of Medicine, on an initiative to promote patient safety through accessible medication information (DailyMed Initiative). The electronic submission of the

content of labeling will allow the agency to provide the DailyMed system with labeling in a comprehensive, reliable, and structured format. The DailyMed can then use this information to make information on medications available to the public. Consumers, health professionals, and others may use this information in several ways, including to identify drug interactions, contraindications, and possible adverse reactions.

(Comment 15) Some comments suggested that the use of electronic labeling may lead to improvement in the communication between the agency and industry when the review division requests modifications for proposed labeling changes. Specifically, the comments referred to word processing software available for tracking changes and editing documents. In addition, the comments suggested that the use of a secure electronic mail exchange system between applicants and the agency during labeling negotiations could be beneficial.

(Response) We appreciate the suggestion and our guidance document entitled "Providing Regulatory Submissions in Electronic Format—NDAs," currently describes submission of the content of labeling in a word processing format in addition to PDF to support editing changes. As mentioned in the proposed rule, PDF is the only type of electronic file format that we have the ability to process, review, and archive because it is currently the most cost effective and best meets our needs for word-for-word comparisons of files. As for any direct communication between applicants and FDA requiring the editing of specific content of labeling, the guidance notes the utility of also submitting labeling in word processing format to facilitate this editing process. In addition, we are looking into new technologies to improve the methods for exchanging and reviewing labeling changes.

E. Providing Labeling to FDA in Electronic Format

(Comment 16) Two comments requested clarification on how to provide labeling with annual reports. They state that some of the confusion with the annual report labeling is because of the lack of a published guidance document on the submission of annual reports in electronic format. The comments also asked if the hard copy information submitted with annual reports containing electronic labeling (distribution, chemistry, manufacturing and controls, preclinical/clinical) should be submitted to the respective reviewing divisions, the central document room, or both.

(Response) As explained previously, the agency has issued guidance for the electronic submission of NDAs, ANDAs, and BLAs. Although there is no published guidance specifically on providing labeling with annual reports, submission of that labeling is covered by these other agency guidance documents on electronic submissions. Therefore, the content of labeling submitted with annual reports would be prepared and submitted electronically as described in the following FDA guidance documents: (1) "Providing Regulatory Submissions in Electronic Format—General Considerations," (2) "Providing Regulatory Submissions in Electronic Format—NDAs," and (3) "Providing Regulatory Submission in Electronic Format—ANDAs" (see section I for a description of these guidance documents).

It should be noted that this final rule only applies to the electronic submission of the content of labeling. It does not address the electronic submission of annual reports generally or any other part of an application. To the extent that the commentors asked for more detailed information about annual report submissions, applicants should continue following the regulations and guidance documents pertaining to those submissions.

(Comment 17) One comment requested harmonization of all elements of annual reports for NDAs, ANDAs, and BLAs.

(Response) As noted previously, the content of the annual report, other than labeling, is not affected by this regulation. However, the labeling submitted with an annual report will be prepared and submitted electronically in the same fashion as described for other electronic labeling submissions in an application (i.e., original labeling submissions in an NDA, ANDA, or BLA).

(Comment 18) One comment requested that Form FDA 2567 not be required with each labeling component submitted to a BLA because CDER does not require that such a form accompany labeling.

(Response) The agency agrees that Form FDA 2567 is not required when submitting BLA labeling electronically using form 356h (Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use). The form should only be used for human blood and blood components (The human blood and blood components circular is not covered by this rule. See comment 6 in section III of this document.)

(Comment 19) Generally, the comments supported our flexible approach regarding the acceptable content of labeling file format. The comments recognized that a flexible approach would enable the industry and FDA to take advantage of future improvements in computer technology and software design. They also agreed with the proposal to describe the method for submitting the content of labeling in guidance, but requested that FDA guidance accompany the final rule. Some comments, however, made suggestions for the use of specific technologies. In addition, we were requested to limit changes to the file format or software specifications.

(Response) Currently, guidance on the submission of labeling is included in the guidance for industry series "Providing Regulatory Submissions in Electronic Format" (see section I of this document). We understand that changes to the file format or software can lead to costly changes in the information technology systems used by industry. For this reason, we plan to limit future changes to those that can lead to increased benefits for both the agency and industry. As mentioned in section II of this final rule, the agency will not switch to new format or software until it is widely available.

(Comment 20) One comment asked that we identify the software used for working on an applicant's labeling (e.g., to compare texts) and whether the software is commercially available or proprietary.

(Response) Currently, the reviewers use Adobe Acrobat and Microsoft Word for reviewing labeling. Both are commercially available. As new technology is developed and we change the software used in reviews, we will make this information available to the public.

F. Part 11 Requirements for Electronic Submissions

(Comment 21) We received a number of comments related to the proposed exemption of the submission of electronic labeling from specific controls under §§ 11.10 and 11.30. Most of the comments were positive and supported the rationale for the exemptions. One comment, however, raised concerns about the effect of the proposed exemptions from part 11 requirements on the integrity of part 11 generally.

(Response) We have recently articulated our current thinking on part 11 in the draft guidance document entitled "Part 11, Electronic Records; Electronic Signatures—Scope and Application" (part 11 draft guidance) issued in the **Federal Register** of February 25, 2003 (68 FR 8775). Among other things,

this part 11 draft guidance announces the agency's intent to exercise enforcement discretion in the manner specified in the draft guidance with respect to the specific part 11 requirements of validation (§ 11.10 (a)), copies of records (§ 11.10(b)), record retention, audit trails (§ 11.10(e) and (k)(2)), and any corresponding requirements in § 11.30. This final rule exempts the electronic submission of labeling content from the requirements of § 11.10(a), (c) through (h), and (k), and the corresponding requirements of § 11.30.

We recognize that there are some differences with respect to the exemptions from part 11 requirements provided in this final rule (i.e., § 11.10(a), (c) through (h), and (k), and the corresponding requirements of § 11.30), and the part 11 requirements set forth in the part 11 draft guidance for which the agency intends to exercise enforcement discretion (i.e., § 11.10(a) through (c), (e), and (k)(2), and any other corresponding requirements in 11.30)). Although the final rule does not provide an exemption from § 11.10(b), the part 11 draft guidance announces that we intend to exercise enforcement discretion with respect to that section in the manner described in the draft guidance.

The exemptions in the final rule and the part 11 requirements for which we intend to exercise enforcement discretion, as described in the part 11 draft guidance, differ because the final rule is specific to the electronic submission of labeling content for human prescription drugs and certain biologics, and the part 11 draft guidance applies to the maintenance of all electronic records and to all electronic submissions subject to part 11.

We exempted the submission of electronic labeling content from certain part 11 requirements because we believe these part 11 requirements are not critical to ensure the quality of the content of labeling submitted under this

rule and we want to ensure that industry resources are not being spent on unnecessary controls. For example, validation for the system used to generate the labeling record is not necessary because the applicant's verification that the information in the labeling record is accurate serves the same objective. Our review of the content of labeling is based on the version of the labeling record submitted to us. Earlier versions of the record, as well as changes made to the earlier versions, are not relevant to our analysis. Thus, other controls related to the creation, modification, and maintenance of the labeling records are also not needed.

IV. 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 section 122, Public Law 105–115, 111 Stat. 2322 (21 U.S.C. 355 note).

V. Paperwork Reduction Act of 1995

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

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

Description: FDA is amending its regulations governing the format in which certain labeling is required to be submitted for review with NDAs, certain BLAs, ANDAs, supplements, and annual reports. The final rule requires that the content of labeling for prescription drug and biological products required under § 201.100(d)(3) be submitted to FDA electronically in a form that we can process, review, and archive. Copies of product labeling are currently required to be submitted to FDA 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. Copies of labeling may be submitted electronically or on paper. The agency is adding the new requirements because submitting the content of labeling in electronic format will simplify the drug labeling review process and speed up the approval of labeling changes.

As required under section 3506(c)(2)(B) of the Paperwork Reduction Act, FDA provided an opportunity for public comments on May 3, 2002 (67 FR 22367), on the information collection provisions of the proposed rule. FDA received two comments stating that the agency underestimated the time and costs to prepare the content of labeling in electronic format for submission to FDA. Specifically, the comments stated that the 15 minutes to convert the labeling into PDF was underestimated because it did not take into account the time needed to proofread the content of labeling document.

FDA believes that proofreading is not an additional cost for submitting labeling in electronic format for new submissions of NDAs, BLAs, and ANDAs. Labeling is proofread prior to submission regardless of the format. If the labeling is in a word processing file, it is irrelevant whether the document is printed or converted to a PDF file. This is because the finished product,

the labeling, is proofread for quality assurance in either case. We also note that someone may need even less time to proofread an electronic file than a printed document because the computer could assist in finding errors. As such, we are not changing the burden estimate for these applications in the final rule.

However, we agree that we should allow for proofreading of labeling under certain circumstances. Applicants that have previously submitted labeling in paper format in annual reports or supplements, but also maintained the labeling document in electronic format, should be provided time for proofreading the converted file. This category of labeling would not require any changes to the labeling since it was last submitted to the agency. It only requires additional time for proofreading to ensure that the electronic document being submitted is the same as the labeling previously submitted in paper format. 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 and supplements) will be approximately 5 hours. We discuss this new category of reporting in more detail in this section V when we calculate the burdens associated with submission of electronic labeling in supplements and annual reports. We also add sections to the estimated annual reporting burden chart to report the burdens.

As we noted in the proposed rule, we recognize that some older annual reports may require additional steps, such as accessing the labeling in the archives, putting the content of labeling into an electronic format, and converting it to a PDF file. In response to the proofreading comments mentioned previously, we are allowing an additional 2 hours for proofreading

this type of labeling (the proposed rule allowed for 8 hours and the final rule is allowing for 10 hours).

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 FDA, and this collection of information was approved by OMB until March 31, 2005, 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 August 31, 2005, under OMB control number 0910–0338 (this includes the collection of information previously approved by OMB under control number 0910–0315). 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 these applicants (respondents) will submit approximately 85 NDAs, 323 ANDAs, and 17 BLAs each year that will be subject to this rule.[10] 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 additional time necessary for submission of the content of labeling

[10] The numbers in this final rule have changed from the proposed rule because we have updated the numbers to be more current.

in electronic format for these applications, will be less than 15 minutes. Therefore, we estimate that respondents will spend approximately 106 hours per year submitting the content of labeling to us in accordance with the final 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 20 BLA applicants (respondents) submit supplements to approved applications to us annually. We estimate that these applicants (respondents) will submit approximately 630 NDA supplements, 1,000 ANDA supplements, and 20 BLA supplements each year that will be subject to this rule.

Based on our experience with voluntary electronic submissions and our knowledge of the drug and biologic industries, we assume that approximately 254 NDA supplements, 396 ANDA supplements, and 10 BLA supplements will be submitted by applicants who 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 165 hours per year submitting the content of labeling to us in these supplements under the final rule.

As mentioned previously, we are adding a new category to the paperwork section to allow for proofreading the converted file of labeling that was previously submitted in supplements in paper form (and not requiring any changes since it was last submitted), but is also maintained by the applicant

in an electronic format. We estimate that approximately 376 NDA supplements, 604 ANDA supplements, and 10 BLA supplements will be submitted by applicants who previously submitted labeling in paper, but have such labeling available in electronic format. We estimate that the hours per response, i.e., the time it will take an applicant to submit the labeling content electronically for these supplements, will be approximately 5 hours. Therefore, we estimate that in the first year, respondents will spend approximately 4,950 hours submitting the content of labeling that was previously submitted in supplements in paper form. For all supplements combined, we estimate that in the first year, respondents will spend approximately 5,115 hours submitting the content of labeling to us in supplements under the final rule. This expenditure of time will only be necessary the first time that a supplement 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 supplements 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 413 hours per year submitting the content of labeling in supplements.

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 275 NDA applicants, 275 ANDA applicants, and 75 BLA applicants (respondents) submit annual reports to us annually. We also estimate that each NDA applicant submits to us approximately 9.45 annual reports, each ANDA applicant submits approximately 16.18 annual reports, and each BLA applicant submits approximately 1 annual report 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 2,600 NDA annual reports, 4,450 ANDA annual reports, and 75 BLA annual reports.

Based on our experience with voluntary electronic submissions and our knowledge of the drug and biologic industries, we estimate that approximately 24 percent of NDA annual reports (624 NDA annual reports), 20 percent of ANDA annual reports (890 ANDA annual reports), and 24 percent of BLA annual reports (18 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 9.45 annual reports, each ANDA applicant submits approximately 16.18 annual reports, and each BLA applicant submits approximately 1 annual report each year. Therefore, approximately 66 NDA applicants, 55 ANDA applicants, and 18 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. Therefore, we estimate that respondents would spend approximately 383 hours per year submitting the content of labeling to us in these annual reports under the final rule.

As mentioned previously, we are adding a new category to the paperwork section to allow for proofreading the converted file of labeling that was previously submitted in annual reports in paper form (and not requiring any changes since it was last submitted), but is also maintained by the applicant in an electronic format. For applicants to include labeling content in their

annual reports in electronic format, we estimate that approximately 36 percent of NDA annual reports (936 NDA annual reports), 30 percent of ANDA annual reports (1,335 ANDA annual reports), and 36 percent of BLA annual reports (27 BLA annual reports) will be submitted by applicants who previously submitted labeling in paper, but have such labeling available in electronic format. As discussed above, we estimate that each NDA applicant submits to us approximately 9.45 annual reports, each ANDA applicant submits approximately 16.18 annual reports, and each BLA applicant submits approximately 1 annual report each year. Therefore, under the final rule, approximately 99 NDA applicants, 83 ANDA applicants, and 27 BLA applicants would need additional time to proofread these annual reports. 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 5 hours. Therefore, we estimate that respondents would spend approximately 11,490 hours per year submitting the content of labeling to us in these annual reports under the final rule.

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. For applicants to include labeling content in their annual reports in electronic format, we estimate that approximately 40 percent of NDA annual reports (1,040 NDA annual reports), 50 percent of ANDA annual reports (2,225 ANDA annual reports), and 40 percent of BLA annual reports (30 BLA annual reports) will be submitted by applicants who may need to access the labeling in their archives, put the content of labeling into an electronic format, and convert it to a PDF file. As discussed previously, we estimate that each NDA applicant submits to us

approximately 9.45 annual reports, each ANDA applicant submits approximately 16.18 annual reports, and each BLA applicant submits approximately 1 annual report each year. Therefore, under the final rule, approximately 110 NDA applicants, 137 ANDA applicants, and 30 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 10 hours.[11] Therefore, we estimate that respondents would spend approximately 32,950 hours per year submitting the content of labeling to us in these annual reports under the final rule.

We estimate that in the first year, respondents will spend approximately 44,823 hours submitting the content of labeling to us in annual reports under the final 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 1,781 hours per year submitting the content of labeling in annual reports.

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

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Responses	Hours per Response	Total Hours
Applications: 314.50	83	1.02	85	.25	21
314.94	117	2.76	323	.25	81

[11] The number increased from 8 hours to 10 hours to allow for additional time to proofread.

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

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Responses	Hours per Response	Total Hours
601.14 (Applications submitted under § 601.2)	17	1	17	.25	4
Subtotal, applications					106
Supplements: 314.70 (Products not requiring additional steps for electronic submission)	167	1.52	254	.25	63
314.70 (Products requiring additional proofreading)	251	1.50	376	5	1,880
314.97 (Products not requiring additional steps for electronic submission)	61	6.50	396	.25	99
314.97(Products requiring additional proofreading)	91	6.50	604	5	3,020
601.14 (Supplements submitted under § 601.12(f)(1) and (f)(2))(Products not requiring additional steps for electronic submission)	8	1.25	10	.25	3
601.14 (Supplements submitted under § 601.12(f)(1) and (f)(2)) (Products requiring additional proofreading)	12	.83	10	5	50
Subtotal, supplements, year one					5,115
Subtotal, supplements, subsequent years[2]					413
Annual Reports: 314.81 (Products not requiring additional steps for electronic submission)	66	9.45	624	.25	156
314.81 (Products requiring additional proofreading)	99	9.45	936	5	4,680
314.81 (Products requiring additional steps for electronic submission)	110	9.45	1,040	10	10,400
314.98 (Products not requiring additional steps for electronic submission)	55	16.18	890	.25	222
314.98 (Products requiring additional proofreading)	83	16.18	1,335	5	6,675
314.98 (Products requiring additional steps for electronic submission)	137	16.18	2,225	10	22,250
601.14 (Annual reports submitted under § 601.12(f)(3) not requiring additional steps for electronic submission)	18	1	18	.25	5
601.14 Annual reports submitted under § 601.12(f)(3) (Products requiring additional proofreading)	27	1	27	5	135
601.14 (Annual reports submitted under § 601.12(f)(3) requiring additional steps for electronic submission)	30	1	30	10	300
Subtotal, annual reports, year one					44,823
Subtotal, annual reports, subsequent years[3]					1,781
Total, year one					50,044
Total, subsequent years[3]					2,300

[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 $2.3 million (see section VIII 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 5 hours per response in the first year. We estimate that in subsequent years respondents will spend less than 15 minutes per response for all supplements.

[3] We estimate that for certain annual reports, respondents will spend either 5 or 10 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 section 3507(d) of the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d)), the agency has submitted a copy of this rule to OMB for its review and approval of these information collections.

The information collection provisions in this final rule have been approved under OMB control number 0910–0530. This approval expires on November 30, 2006. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless the information collection displays a currently valid OMB control number.

VI. Environmental Impact

The agency has 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.

VII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the 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, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

VIII. Analysis of Economic Impacts

We have examined the impacts of this final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), 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 final rule is consistent with the regulatory philosophy and principles identified in Executive Order 12866 and in these two statutes. The final rule is a significant regulatory action as defined in section 3 paragraph (f)(4) of the Executive order. However, as shown in this section VIII, the final 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 final rule because the final 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 final rule 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 of approved and new NDAs, BLAs, and ANDAs to convert the content of labeling to an electronic format for submission. At this time, PDF is the type of electronic file format that we have the ability to accept for processing, reviewing, and archiving. 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.

Three comments were received regarding the economic impact analysis. Two of these comments suggested that the cost to convert the content of labeling to a PDF format was underestimated because it did not include the cost to proofread the labeling after it is converted to a PDF file. The time required for proofreading ranged from 4 to 6 hours depending on the complexity/length of the labeling. One of these comments also suggested that the cost for converting older labeling that is only available on paper was underestimated, suggesting that the costs should include costs for equipment, training, and time to scan paper documents.

The agency agrees that we should allow for proofreading of labeling under certain circumstances. Applicants that have previously submitted annual reports or supplements in paper form, but also maintained the documents in electronic format, should be provided time for proofreading the converted file. This category of labeling would not require any changes to the labeling since it was last submitted to the agency. It only requires additional time for proofreading to ensure that it is the same as the labeling submitted in paper format. Five hours was used in this analysis to reflect the cost under these circumstances.

However, we do not agree that proofreading is an incremental cost for labeling that has been changed and is in a word processing file. Proofreading of the finished product for submission (in this case, the PDF file) is done now as part of current industry quality assurance practice. We also do not agree with the comment that costs for scanning labeling should be included in the impact analysis. While scanning paper labeling and using optical character recognition software is an option some firms may choose, it is not required. The labeling can be transcribed into a word processing format and then converted. However, we did increase the time estimate for such conversions by an additional 2 hours and we also increased our estimate of the percent of labeling that is included in this category because we now believe that number was underestimated.

Annually, we receive approximately 425 applications, 7,125 annual reports, and 1,650 supplements that contain labeling from approximately 625 applicants. Based on our experience working with voluntary electronic submissions, we estimate that overall approximately 70 percent of the applicants (440) already have the necessary software and trained personnel to

comply with this rule. The remaining 30 percent of applicants (190) would need to purchase software, which costs about $250. Based on agency review, approximately 78 percent of these 190 applicants 148 would be considered small (fewer than 750 employees for drug product manufacturers and 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 148 copies. The remaining 22 percent of applicants (42) 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 126 copies (42 x 3). Thus, the total one-time cost for software is $68,500 ((148 + 126) 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 (548 employees), for a total one-time cost of $213,720 (($150 + (6 hours x $40)) x 548). The total one-time cost for software and training combined is estimated to be $282,220 ($68,500 + $213,720).

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. The PDF file, being the finished product, would be proofread for quality assurance. Annually, we receive approximately 1,650 supplements that would be subject to the final rule. Because 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. Currently, the labeling in about 40 percent (660) of the supplements received is submitted in a PDF

format and would require an estimated additional 15 minutes to comply with this final rule. The labeling in the remaining 60 percent (990) will require an estimated 5 hours to process and proofread. Thus, the total number of hours needed to convert applicable labeling in supplements to a PDF file format is 5,115 ((0.25 x 660) + (5 x 990)).

Labeling in most of the annual reports will also need to be converted. The conversion of this labeling to a PDF file for about 40 percent of NDA annual reports (975), 50 percent of ANDA annual reports (2,295), and 40 percent of BLA annual reports (40), 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 10 hours to complete, for a total of 33,100 hours ((975 + 2,295 + 40) x 10). For the content of labeling in the remaining annual reports (3,815), an estimated 40 percent (1,526) would require 15 minutes to process because they are currently in PDF format, and the remaining 2,289 annual reports will require approximately 5 hours to process and proofread, for a total of 11,827 hours ((1,526 x 0.25) + (2,289 x 5)). Thus, the total number of hours needed to convert all applicable labeling to a PDF file format in supplements and annual reports is 50,042 (5,115 + 33,100 + 11,827). 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 about $2.0 million (50,042 x $40). The cost for the entire rule is estimated to be about $2.3 million ($0.3 million (software and training + $2.0 million labeling)).

Approximately 300 domestic entities would be affected by this final rule, about 240 of which meet the Small Business Administration's definition of a small entity (fewer than 750 employees for drug product manufacturers and fewer than 500 employees for biological product manufacturers). The economic

impact of this final 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 7 applications, and, assuming a worst case scenario—the firm did not have the content of labeling in an electronic format and needed to purchase software and train employees—this rule would cost the average small firm about $4,000 ($1,030 software and training + (7 x 10 hours x $40)), which is about $550 per application. Because these costs would almost certainly be less than 1 percent of product revenues, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities.

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, 21 CFR parts 314 and 601 are amended as follows:

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

■ 1. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 355a, 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 (l)(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: 7/31/03

July 31, 2003.

Jeffrey Shuren,
Assistant Commissioner for Policy.

[FR Doc. 03–????? Filed ??–??–03; 8:45 am]

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