

“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 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 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.”

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).

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.