

problems associated with public health or animal safety. According to the comment, the requirement of reporting product/manufacturing defects, other than serious ones, is not consistent with FDA's statement. The comment requested that 21 CFR

514.80(b)(4)(iv)(A) refer only to ADEs.

FDA declines to make the proposed change because eliminating the provision as requested would leave a significant gap in the safety and effectiveness profile of a drug product. The agency would no longer receive information for product and manufacturing defects that may result in "nonserious" but significant unexpected adverse drug events, i.e., events not listed on the label of a particular drug product. These could include new symptoms and pathophysiologically-related events such as increases in enzymes or blood counts that appear not to be serious by definition, but could negatively impact the effect of the drug product. Further, the applicant would not have to report product and manufacturing defects that may result in a lack of expected effectiveness.

*O. Periodic Drug Experience Report—Adverse Drug Experiences in the Literature (§ 514.80(b)(4)(iv)(B))*

(Comment 23) One comment stated that applicants routinely have not submitted ADEs separate from the literature. According to the comment, applicants have limited ability to investigate incidents such as studies conducted by unrelated third parties. The comment requested that this section be deleted or reworded to clarify FDA's intent.

FDA is not requesting that each individual ADE in the literature be submitted on Form FDA 1932. The use of Form FDA 1932 does not apply to § 514.80(b)(4)(iv)(B). As the rule states, FDA is asking that "a bibliography of pertinent references" of the literature containing ADEs be submitted. A bibliographic listing from Medline or other database searches would be acceptable.

*P. Periodic Drug Experience Report—Adverse Drug Experiences Occurring in Postapproval Studies That Are Not Previously Reported (§ 514.80(b)(4)(iv)(C))*

(Comment 24) One comment noted that reporting ADEs from postapproval studies is duplicate reporting given that the study report is submitted to ONADE. The comment contended that this would be a considerable additional workload, especially for the first 2 years postapproval. Also, if this reporting requirement is not changed, the

comment asked if FDA wanted these reports on Form FDA 1932. FDA disagrees that this would be additional work. This requirement only pertains to ADEs not previously reported to CVM. Any study reports previously submitted to ONADE do not have to be submitted again. Applicants are not required to submit these experiences on Form FDA 1932.

*Q. Other Reporting—Advertisements and Promotional Labeling (§ 514.80(b)(5)(ii))*

(Comment 25) One comment stated that the regulation is not clear about the submission requirements for OTC and Rx promotional labeling. Further, the comment requested that the promotional labeling requirement be applicable to Rx products only, in accordance with current regulations.

FDA believes that the regulation is clear about the submission requirement for OTC and Rx labeling. FDA declines to change the applicability to Rx products only. This is not a new proposal; it was included in the proposed rule for records and reports.

*R. Other Reporting—Distributor's Statement—Current Product Labeling (§ 514.80(b)(5)(iii)(A)(1))*

(Comment 26) One comment suggested that, with regard to distributor's labeling, the qualifying phrase should not be limited to "manufactured for" or "distributed by." The comment argued that § 201.1(h)(5) (21 CFR 201.1(h)(5)) provides the appropriate alternatives, which should also be permitted, and recommended that the last sentence in this section be changed.

The agency concurs with the proposed revision and has revised this section.

The following is the change to § 514.80(b)(5)(iii)(A)(1):

(1) The distributor's labeling must be identical to that in the approved NADA/ANADA except for a different and suitable proprietary name (if used) and the name and address of the distributor. The name and address of the distributor must be preceded by an appropriate qualifying phrase as permitted by the regulations such as "manufactured for" or "distributed by."

*S. Other Reporting—Distributor's Signed Statements (§ 514.80(b)(5)(iii)(B)(2) and (b)(5)(iii)(B)(3))*

(Comment 27) One comment noted that the current regulation § 514.8(a)(6)(iii) (21 CFR 514.8(a)(6)(iii)) requires the distributor to state that he/she will distribute the drug only under its approved labeling and that any other

labeling or advertising will prescribe, recommend, or suggest use only under the approved labeling. According to the comment, § 514.80(b)(5)(iii)(B)(2) and (b)(5)(iii)(B)(3) of the interim final rule omits the limitation on promotional labeling. The comment suggested that the language of 21 CFR 514.8(a)(6)(iii) be changed so that paragraph (b)(5)(iii)(B)(3) would read as follows: "(3) that the distributor will distribute the product only for use under the conditions stated in the approved labeling, and any other labeling or advertising will prescribe, recommend, or suggest its use only under the approved labeling."

The agency believes that the provisions of paragraph (b)(5)(iii)(B)(3) of the proposed rules are similar to those of § 514.8(a)(6)(iii), but have been simplified and written in plain language. However, to make the meaning clear, the agency has revised the section by replacing the word "advertise" with "promote."

The following is the change to § 514.80(b)(5)(iii)(B)(3):

"(3) That the distributor will promote the product only for use under the conditions stated in the approved labeling;"

*T. Multiple Applications—Information Specific to a Particular NADA/ANADA (§ 514.80(c)(4))*

(Comment 28) One comment stated that the requirements under "Multiple Applications" do not appear to decrease, but may increase the burden on the applicant. In particular, the comment questioned the requirement under § 514.80(c)(4) and requested clarification. The comment also expressed concern with the increased reporting burden due to the increasing number of approved combinations of drugs for use in feeds since the implementation of the ADAA. Further complicating the reporting issue is that frequently there are nonapplicants involved in the marketing of these combinations. The comment stated that, with the exception of "promotional literature," there is rarely any other information to be reported. The comment suggested that the "promotional literature" be submitted to the application held by either party—i.e., the nonapplicants or applicant—and not the application approved for the use of the combination of drugs.

The provision of the regulation in question is currently codified under § 510.300(b)(4)(ii). The current regulation and the proposal in the interim final rule are similar. There is no increase of the reporting burden. It is not the intention of FDA for the