

with § 510.300 and will increase the number of reports.

The burden for reporting domestic and foreign ADEs is the same under § 510.300. Foreign ADEs are required to be reported under the current regulations, although this requirement is not stated as explicitly in the current regulation as under § 514.80(a)(2). FDA is adding the language concerning foreign sources in order to make the rule more clear.

(Comment 16) One comment requested that applicants should not have to report cases where the reporter believes that an event is not drug related and the reporter does not want the case to be filed with FDA.

The ADE must be reported regardless of whether or not the reporter considers it to be drug related, if it meets the definition of an ADE (see 21 CFR 514.3), or whether a caller wishes it not to be reported. FDA will provide assistance on a case-by-case basis for specific incidences that the applicant or other reporter still believes should be excluded.

I. Nonapplicant Report (§ 514.80(b)(3))

(Comment 17) One comment recommended that in order to avoid confusion and over-reporting, all ADE reports should be submitted to CVM by the applicant, and that the sentence “if the nonapplicant elects to also report directly to FDA, the nonapplicant should submit the report on Form FDA 1932 within 15 working days of first receiving the information” should be deleted from the regulation. The comment maintained that if the nonapplicant reports to FDA in the 15-day period and it is determined by the applicant that it is not a serious, unexpected event, FDA might come to the conclusion that the applicant is under-reporting.

FDA does not concur with this recommendation. FDA believes that it is important for the nonapplicant to have a mechanism to report voluntarily. FDA will evaluate any nonapplicant report it receives to determine whether the report is of a serious, unexpected ADE.

J. Periodic Drug Experience Report—Distribution Data (§ 514.80(b)(4)(i))

(Comment 18) One comment questioned the need to report distribution data on the amounts of product exported outside the United States, and if the data are to be reported, how they will be used. The comment stated that since foreign ADEs are not required to be reported, there is no benefit for reporting amounts exported.

Foreign reports have to be submitted under § 514.80. Foreign ADEs for the

U.S.-approved application must be submitted under § 514.80(b)(2) or (b)(4)(iv). These data will be used in a similar manner as domestic distribution data in determining if an increased frequency of ADE exists.

K. Periodic Drug Experience Report—Nonclinical Laboratory Studies and Clinical Data Not Previously Reported (§ 514.80(b)(4)(iii))

(Comment 19) One comment maintained that studies conducted to support a future claim should not be reported in the periodic drug experience report. The comment suggested that because sponsors make submissions to CVM's Office of New Animal Drug Evaluation (ONADE) for its review, and also report to CVM's Office of Surveillance and Compliance, the confusion could be eliminated by changing the title of this section from “Nonclinical laboratory studies and clinical data not previously reported” to “Nonclinical laboratory studies and clinical data not previously submitted.”

FDA believes that such a change is not necessary. This requirement only pertains to data not previously reported to CVM, including submissions to ONADE and reports to the Office of Surveillance and Compliance.

L. Periodic Drug Experience Report—Nonclinical Laboratory Studies and Clinical Data Not Previously Reported—Prepublication Manuscripts (§ 514.80(b)(4)(iii)(C))

(Comment 20) One comment questioned the value and need to submit prepublication manuscripts and strongly recommended deletion of this requirement. The comment stated that such manuscripts are no better than draft reports and submission of these to entities other than the publisher may be prohibited by a journal in its publication policy. Additionally, it stated that the applicant could comply with the requirements for submission of a study within 1 year of its completion only when the study is conducted by or for the applicant.

FDA concurs with the recommendation and has revised this section of the regulation.

The following is the change to § 514.80(b)(4)(iii)(C):

(C) Descriptions of completed clinical trials conducted by or for the applicant must be submitted no later than 1 year after completion of research. Supporting information is not to be reported.

M. Periodic Drug Experience Report—Adverse Drug Experiences (§ 514.80(b)(4)(iv))

(Comment 21) One comment stated that FDA limited the scope of a manufacturing/product defect by changing the definition in § 514.80(g) in response to comment 12 of the interim final rule. The comment stated, “the scope of what is considered to be a manufacturing/product defect has now been limited to that which is a problem associated with public health or animal safety or that is a significant, chemical, physical, or other change or deterioration in the drug product or significant defective packaging or labeling error.” According to the comment, nonsignificant defects, which involve the physical appearance but have no impact on animal safety or public health, do not need to be reported since these defects are not included in the definition of manufacturing/product defects. The comment provided a specific example of a blister unit with a misaligned die-cut of a blister, which does not affect the integrity of the package seal or labeling or an empty blister well.

Manufacturing/product defects are defined in § 514.3. If a problem with the product does not fall under the definition in § 514.3, then it is not considered a manufacturing/product defect. The example of a misaligned die-cut of a blister unit may or may not be considered a manufacturer/product defect depending on whether it is or is not a deviation of a distributed product from the standard specified in the approved application or any other portion of the definition.

Manufacturing/product defects that may result in a serious adverse drug event must be submitted as a 3-day NADA/ANADA field alert report. The requirement of a serious adverse drug event limits the number of 3-day reports. Nonserious manufacturing/product defects should be submitted in the periodic drug experience report. The manufacturing/product defects definition given in § 514.3 does not pertain to the good manufacturing practice (GMP) regulations or other regulations outside of § 514.80.

N. Periodic Drug Experience Report—Adverse Drug Experiences Not Previously Reported (§ 514.80(b)(4)(iv)(A))

(Comment 22) One comment suggested that product/manufacturing defects, other than serious ones, should not have to be reported. FDA stated in the preamble of the interim final rule that FDA would limit its scope to