

*C. Definition of Increased Frequency of Adverse Drug Experience and Summary Report of Increased Frequency of Adverse Drug Experience (§§ 514.3 and 514.80(b)(2)(iii))*

(Comment 3) One comment requested that FDA provide additional clarification of this requirement or delete the requirement of a summary report. The comment acknowledged and appreciated FDA's willingness to make changes in response to previous comments. However, it stated that there are doubts that this requirement can be met "even with the adjustment for drug exposure." The comment stated that the adjustment for drug exposure based on distribution data would be unreliable given that distribution data does not "equate[d] with the amount actually used (exposure) in any given time period." Also, the comment maintained that this requirement of a summary report is "troubling" because it is required to be submitted within 15 working days.

In retrospect, FDA does concur with the concern about requiring summary reports within 15 working days. FDA has modified § 514.80(b)(2)(iii) to require that information be reported in the 6-month and yearly periodic drug experience reports under § 514.80(b)(4)(v). FDA also has made a conforming change to § 514.80(a)(4) to include § 514.80(b)(4)(v).

The following is the change to former § 514.80(b)(2)(iii), now under § 514.80(b)(4)(v):

(v) *Summary report of increased frequency of adverse drug experience.* The applicant must periodically review the incidence of reports of adverse drug experiences to determine if there has been an increased frequency of serious (expected and unexpected) adverse drug events. The applicant must evaluate the increased frequency of serious (expected or unexpected) adverse drug events at least as often as reporting of periodic drug experience reports. The applicant must report the increased frequency of serious (expected and unexpected) adverse drug events in the periodic drug experience report. Summaries of reports of increased frequency of adverse drug events must be submitted in narrative form. The summaries must state the time period on which the increased frequency is based, time period comparisons in determining increased frequency, references to any previously submitted Form FDA 1932, the method of analysis, and the interpretation of the results. The summaries must be submitted in a separate section within the periodic drug experience report.

The following is the change to § 514.80(a)(4):

"(4) The requirements of this section also apply to any approved Type A medicated article. In addition, the

requirements contained in § 514.80(b)(1), (b)(2), (b)(4)(iv), and (b)(4)(v) apply to any approved Type A medicated article incorporated in animal feeds."

*D. Definition of Serious Adverse Drug Experience (§ 514.3)*

(Comment 4) One comment asked FDA to change the definition of a "Serious adverse drug experience" from "an adverse event that is fatal or life threatening, requires professional intervention." to "an adverse event that is fatal or is a life-threatening event that requires professional intervention." The comment stated that the listing of events "adds confusion as to whether all or just one of the conditions need to be present for the event to meet the definition of serious." The comment questioned whether "professional intervention" is necessary for every listed condition in the definition for the event to be considered a serious ADE. Another comment asked that "requires professional intervention" be removed from the list since some events involving veterinary intervention are not serious.

In order to clarify the issue, FDA has added "or" between each term so that it is clear that each event listed is independent of any other event. Any one of the events listed will be considered a serious ADE. Both comments suggest that the ADE be considered serious only in the case where the fatal or life-threatening event requires professional intervention. FDA believes that a fatal or life-threatening event is serious regardless of whether professional intervention is sought for treatment. Thus, FDA will not change the definition to require professional intervention for each event. Events that are life threatening or that require professional intervention will be considered serious ADEs. FDA believes that any professional veterinary intervention is serious enough in nature to require reporting.

(Comment 5) One comment requested clarification of the portion of the definition that "requires professional intervention" as to whether this means that any reports from veterinarians to the applicant are considered serious.

FDA addressed this issue in comment 10 of the preamble in the interim final rule and added professional intervention to clarify the definition of seriousness for animal drugs. We believe that the definition is appropriate.

(Comment 6) One comment questioned whether "infertility" is a serious ADE. The comment stated that infertility following administration is

rarely drug-related, and that many types of infertility would not be serious.

We disagree with the comment. Purebred producers (e.g., of cats, dogs, or cattle) would not want to use a product that may impair fertility unless necessary. Therefore, FDA believes that it is important to make label changes regarding fertility as quickly as possible, thus providing important labeling information for the end user. FDA will not remove "infertility" from the definition.

(Comment 7) One comment stated that the "unique aspects of evaluating animals that are housed and managed as a group" should be included in the definition. The comment proposed that FDA use the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) definition of serious ADE. The comment used an example situation in which the background frequency of death in animals not treated is higher than animals treated with the drug. FDA addressed a similar issue in the preamble of the interim final rule under comment 7. The VICH guidance documents are in early development, and once completed it is the intention of FDA to adopt and implement them in a manner consistent with its existing regulations. At this time, it is premature to adopt VICH definitions.

(Comment 8) One comment stated that a patient examination should not be considered professional intervention if there is no administration or dispensing of medications. According to the comment, this should not be the sole means of classifying an event as serious. The comment further stated that if there is an examination and no treatment is indicated by the veterinarian, then "professional intervention in the outcome of the case has not occurred."

An examination with no medical or surgical intervention/treatment or any treatment is a reportable ADE. If professional services of a veterinarian are engaged then this is considered an intervention incident. For example, if an over-the-counter (OTC) or prescription (Rx) drug product is given to the animal prior to veterinary intervention and an adverse drug reaction occurs, then the veterinarian, upon examination, may have important information concerning the event. As explained in the preamble of the interim final rule, FDA added the words "professional intervention" to clarify the definition of seriousness for animal drugs. FDA believes that the definition is appropriate.

The following is the change to the definition for "serious adverse drug experience" in § 514.3: