

Richard A. Carnevale  
Vice President, Regulatory, Scientific & International Affairs

3937 '02 APR -3 P1:27

April 3, 2002

Dockets Management Branch  
HFA-305  
Food and Drug Administration  
5630 Fishers Lane, rm. 1061  
Rockville, Maryland 20852

Re: Docket No. 88N-0038 – Records and Reports Concerning Experience  
With Approved New Animal Drugs; Interim final rule

AHI commends the Agency for its perseverance in bringing this rule closer to promulgation and for the improvements reflected in the interim final rule that were made as a result of the comments received from AHI and others. While AHI feels many positive changes have been made, we have some general comments as well as more specific ones directed to certain aspects of the interim final rule. The latter are presented in tabular format with reference to the section of 21 CFR 514 and the language in question.

In general, AHI finds the preamble and the new format and organization of the interim final rule to be helpful.

21 CFR	Item	Comment
514.3(a) (2)	<i>Adverse drug experience</i> is... (2) Failure of a new animal drug to produce its expected pharmacological or clinical effect (lack of effectiveness)	AHI believes that this part of the definition needs to include the qualification given in the preamble on page 5048, comment 7, which recognizes that it is the <i>unusual</i> failure to respond to therapy that is of concern.  For this reason, AHI proposes that the

88N-0038

C16

21 CFR	Item	Comment
	<p>AHI REVISION:                      (2) <u>Unusual</u> failure of a new animal drug to produce its expected pharmacological or clinical effect (lack of effectiveness)</p>	<p>definition be amended to read:                      (2) <u>Unusual</u><sup>1</sup> failure of...</p> <p>We would also note that current product labeling does not usually address efficacy failures, thus the statement “However, if the failure of some individuals to respond to therapy was expected (<i>i.e.</i>, is listed in the labeling), this failure should be submitted in the periodic experience report” could result in these situations being considered to be unexpected, which triggers the 15-day report. See also our comment on 21 CFR 514.3(i) <i>Unexpected drug experience</i>.</p>
514.3(c)	<p><i>Applicant</i> is a person who owns a new animal drug application or an ANADA.</p> <p>AHI REVISION:  <i>Applicant</i> is a person who <u>holds</u> a new animal drug application or an ANADA.</p>	<p>Ownership is a legal, rather than a regulatory, consideration that is not within the purview of the Agency. For example, a parent company or other entity may be the actual owner, but the US company is the sponsor. The preamble on pg 5054 uses more appropriate language: "In the rule, the term "applicant" is limited to the holder of an approved application (NADA or ANADA)...".</p> <p>AHI agrees and urges FDA to change this definition to read:                      “Applicant is a person who <u>holds</u> a new animal drug application or an ANADA”.</p>
514.3(d)	<p><i>Increased frequency of adverse drug experience</i> is an increased rate of occurrence of a particular serious adverse drug event, expected or unexpected, after appropriate adjustment for drug exposure.</p>	<p>AHI appreciates FDA’s willingness to revise this definition in response to concerns raised in our previous comments, however, we continue to have some doubts as to how this can be accomplished, even with the adjustment 'for drug exposure'. Sponsors have only distribution reports to rely on, which cannot be equated with the amount actually used (exposure) in any given time period. FDA needs to provide additional clarification of its intent (<i>i.e.</i>, on what basis this determination is to be made), or delete the requirement. This is especially troubling</p>

<sup>1</sup> Changes (additions) will be underlined throughout our comments.

21 CFR	Item	Comment
		when coupled with the requirement to provide a summary report within 15 days of such a determination (21 CFR 514.80(b)(2)(iii)).
514.3 (h)	<p><i>Serious adverse drug experience</i> is an adverse event that is fatal or life threatening, requires professional intervention, or causes an abortion, stillbirth, infertility, congenital anomaly, prolonged or permanent disability, or disfigurement.</p> <p>AHI REVISION:</p> <p><i>Serious adverse drug experience</i> is an adverse event that is fatal, or <u>is a life-threatening event that</u> requires professional intervention, or causes an abortion, stillbirth, infertility, congenital anomaly, prolonged or permanent disability, or disfigurement.</p>	<p>The changes proposed by FDA are an improvement over the definition in the 1991 proposed rule. AHI is concerned, however, that enumerating the criteria in the manner proposed 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.</p> <p>For example, does “requires professional intervention” mean whenever a veterinarian reports an adverse drug event (ADE) it is considered serious?</p> <p>Does “serious” infer that there was professional intervention (veterinarian) with every listed condition? If a cow aborts and a veterinarian is not contacted, then is this event not considered serious?</p> <p>If some of the conditions listed under “serious” are on the label (expected), are they still considered serious and reported within this 15-day time?</p> <p>For clarity and to reduce reporting as ‘serious’ whenever a veterinarian is involved, AHI requests the definition be changed to read: “...<u>is a life-threatening event that</u> requires professional intervention, or ...”. This modification of the definition then clarifies that it is the life-threatening event and involvement of a profession that makes it serious and reportable in 15 days.</p>
514.3 (i)	<p><i>Unexpected drug experience</i> is an adverse event that is not listed in the current labeling for the new animal drug and includes any event that may be symptomatically and pathophysiologically related to an event listed on the labeling...”</p>	<p>Inclusion of the criterion "is listed in the labeling" as the basis for determining whether the ADE it is an <b>unusual</b> efficacy failure or <b>unexpected</b> adverse experience is a change from the current rule [21 CFR 510.300(b)(2)(i)] that uses the NADA file as the basis for this determination. There is currently very limited information of this</p>

21 CFR	Item	Comment
	<p>AHI REVISION:</p> <p><i>Unexpected drug experience</i> is an adverse event that is not listed in the current labeling for the new animal drug <u>or reported in its Freedom of Information Summary(ies)</u> and includes any event that may be symptomatically and pathophysiologically related to an event listed on the labeling...”</p>	<p>nature on Type A Medicated Article labels and most labels of over the counter drugs. This change then can potentially (a) expand the number of reports required and/or (b) result in added work load for the Center if firms elect to add such information to their labels in order to minimize the impact of this new reporting requirement.</p> <p>An adverse experience may be commonly recognized (thus expected), but may not appear on the label. What is the Center’s expectation under this circumstance?</p> <p>AHI believes that the rationale given on preamble page 5049 that the NADA/ANADA file is not publicly available is inappropriate, because (1) each NADA has a publicly available Freedom Of Information Summary that details the clinical and target animal safety studies, including enumeration of adverse events seen in such studies, (2) sponsors (applicants) are the primary source of ADE reports, and (3) sponsors are the ones responsible for making the initial determination whether the event is unusual or unexpected. There is thus minimal public involvement in such reporting.</p> <p>AHI proposes that the definition be revised to include the FOI Summary as the basis for determination including those resulting in lack of effectiveness, not simply the label alone. The definition would then read: “...that is not listed in the current labeling for the new animal drug <u>or reported in its Freedom of Information Summary(ies)</u>...”.</p>
514.80(a)(1)	<i>Applicability (1)</i> Each applicant and nonapplicant must establish	The requirement for a <b>separate</b> filing system for the required records & reports is new.

21 CFR	Item	Comment
	<p>and maintain indexed, separate, and complete files containing full records of all information pertinent to safety or effectiveness of a new animal drug that has not been previously submitted as part of the NADA or ANADA. Such records must include information from domestic, as well as foreign sources.</p> <p>AHI REVISION:</p> <p><i>Applicability (1)</i> Each applicant and nonapplicant must establish and maintain indexed and complete files containing full records of all information pertinent to safety or effectiveness of a new animal drug that has not been previously submitted as part of as part of <u>an investigational new animal drug (INAD) file</u>, the NADA or ANADA. Such records must include information from domestic, as well as foreign sources.</p>	<p>The 1991 proposal and current regulation [21 CFR 510.300(a)] only require adequately organized and indexed files of full reports. The Center did not explain why such a change is necessary. AHI strongly believes that whether such records are stored as part of another file system or separately is the sponsor's decision to make in view of its circumstances. AHI proposes, therefore, that the word separate be deleted.</p> <p>AHI is also concerned that the criterion 'not previously submitted as part of the NADA or ANADA' would appear to exclude submissions made to INAD files until the INAD is incorporated by reference into the NADA or ANADA file. It raises the question of what information needs to be reported, when, and to whom. Many sponsors elect to develop new claims or provide for administration of the drug to new species or classes of animals by submitting the data to the INAD file for phased review. The Office of New Animal Drug Evaluation (ONADE) as a part of its pre-market review process reviews such reports. It should, therefore, be unnecessary to also provide such reports as part of a periodic drug experience report, or to maintain them as part of such a filing system.</p> <p>AHI proposes that INAD files be included in the criteria such that the phrase reads: "...as part of <u>an investigational new animal drug (INAD) file</u>, the NADA or ANADA".</p>
<p>514.80 (a)(2) and (b)(2)(i)</p>	<p>(a)(2) ...Applicants and nonapplicants must submit data, studies, and other information described in this section from domestic, as well as foreign sources.</p> <p>(b)(2)(i) "<i>Initial report</i>. This report provides information on</p>	<p>AHI requests that FDA confirm that the regulation requires submission of reports of adverse drug experiences spontaneously reported to an applicant in countries other than the U.S. as well those ADEs reported spontaneously in the US. If this is the case, this requirement will require additional resources not only on the part of sponsors, but FDA. The amount of time needed to</p>

21 CFR	Item	Comment
	<p>each serious, unexpected adverse drug event, regardless of the source of the information.”</p>	<p>coordinate foreign reports could be substantial.</p> <p>Foreign experience will also greatly expand what is submitted. What is to be gained by this? Currently, summaries only are submitted for foreign studies in the NADA pre-approval. The burden for post-approval should be not greater.</p>
514.80 (b)(3)	<p><i>Nonapplicant Report.</i>                      Nonapplicants must forward reports of adverse drug experiences to the applicant within 3 working days of first receiving the information...</p> <p>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.</p> <p>AHI REVISION:</p> <p><i>Nonapplicant Report.</i>                      Nonapplicants must forward reports of adverse drug experiences to the applicant within 3 working days of first receiving the information...</p>	<p>It appears that ANY adverse event known to the nonapplicants must be reported to the applicant within 3 days. This is regardless of its serious or non-serious, and expected or unexpected status. This could lead to over-reporting if the nonapplicant decides to do both.</p> <p>The preamble on page 5053 in comment 42 would appear to agree with this concern; however, to avoid confusion and over-reporting, AHI recommends that all ADE reports should be submitted to CVM only by the applicant. 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.</p> <p>Additionally, 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.</p>
514.80(b)(4)(i)	<p><i>Distribution Data...</i> This information must be presented in two categories: quantities distributed domestically and quantities exported.</p>	<p>AHI wonders if foreign ADEs are not required to be reported, why then report quantity exported? Of what benefit is this information to CVM? How will CVM use it?</p>
514.80 (b)(4)(iii)	<p><i>Non-clinical laboratory studies and clinical data not previously reported.</i></p>	<p>AHI believes that studies conducted to support a future claim should not be reported in the periodic drug experience report, unless</p>

21 CFR	Item	Comment
	<p>AHI REVISION:</p> <p><i>Non-clinical laboratory studies and clinical data not previously submitted.</i></p>	<p>or until the sponsor elects to no longer pursue the claim. At that time, only those studies not previously submitted for review should be included in the next periodic drug experience report. To require otherwise would be an extremely onerous and absurd requirement. The preamble on page 5051 in comment 28 appears to agree with this position where it is stated that “We did not intend to require duplicate reporting. To make this explicit, we renamed the section... We included the phrase “not previously reported” in the title to clarify that duplicate reporting is not required.” Because sponsors make <i>submissions</i> to ONADE for their review and <i>reports</i> to the Office of Surveillance and Compliance, the confusion could be eliminated by changing the title of this section to:  <i>Non-clinical laboratory studies and clinical data not previously submitted.</i></p>
<p>514.80                      (b)(4)(iii)                      (C)</p>	<p><i>Non-clinical laboratory studies and clinical data not previously reported.</i></p> <p>(C) Descriptions of, or if available, prepublications manuscripts relating to completed clinical trials conducted by or otherwise known to the applicant. Supporting information is not to be reported. A study must be submitted no later than 1 year after completion of research.</p> <p>AHI REVISION:</p> <p>(C) Descriptions of completed clinical trials conducted by or otherwise known to the applicant. Supporting information is not to be reported. A study <u>conducted</u></p>	<p>AHI questions the value of and need to submit prepublication manuscripts. Such manuscripts are no better than draft reports and submission to entities other than the intended publisher may be prohibited by the journal in its publication policy. AHI strongly recommends deletion of this requirement.</p> <p>Additionally, the applicant can comply with the requirement for submission of a study within 1 year of its completion only when the study is conducted by or for the applicant. This distinction needs to be made in the regulation.</p> <p>AHI, therefore, requests this section to be revised to read:</p> <p>“Descriptions of completed clinical trials conducted by or otherwise known to the applicant. Supporting information is not to be reported. A study <u>conducted by or for the</u></p>

21 CFR	Item	Comment
	<p><u>by or for the applicant</u> must be submitted no later than 1 year after completion of research.</p>	<p><u>applicant</u> must be submitted no later than 1 year after completion of research.”</p>
<p>514.80(B)(4)(iv)(A)</p>	<p><i>Adverse Drug Experiences</i>                      (A) Product/manufacturing defects and adverse drug experiences not previously reported under §514.80(b)(1) and (b)(2) must be reported individually on Form FDA 1932.</p> <p>AHI REVISION:                      (A) Adverse drug experiences not previously reported under §514.80(b)(2) must be reported individually on Form FDA 1932.</p>	<p>Since all “serious” product/manufacturing defects are submitted under the 3-day field alert, the reporting of all other (<i>i.e.</i>, non-serious) product/manufacturing defects in the periodic report is an unnecessary burden that appears to be inconsistent with the Agency’s preamble comments (page 5049, comment 12), where it is pointed out that the definitions for product/manufacturing defect [21 CFR 514.3(g)] have been modified “to limit their scope to problems associated with public health or animal safety”. In addition, non-serious product/manufacturing defects are catalogued by the manufacturer under Good Manufacturing Practice regulations and are available to FDA during routine inspections.</p> <p>AHI suggests, therefore, that the requirement be reworded to refer only to adverse drug experiences: Adverse drug experiences not previously reported under §514.80(b)(2) must be reported individually on Form FDA 1932.</p>
<p>514.80 (b)(4)(iv) (B) and (C)</p>	<p><i>Adverse Drug Experiences</i>                      (B) Reports of adverse drug experiences in the literature must be noted in the periodic drug experience report. A bibliography of pertinent references must be included with the report. Upon FDA’s request, the applicant must provide a full text copy of these publications.</p>	<p>AHI finds these sections to be confusing. Sponsors have not routinely separately submitted adverse drug events from the literature, except as described in the submitted published literature [current 21 CFR 510.300(a)(1) or new 21 CFR 514.80 (b)(4)(iii)(B)]. We wonder whether this requirement applies to serious or unexpected ADEs and, if it does, how CVM expects sponsors to comply. In most cases, the sponsor has little ability to investigate such incidents, particularly in studies conducted by unrelated third parties. AHI, therefore, fails to see what is intended by this section or its necessity. The section should be re-worded to clarify FDA’s intent, or be deleted.</p>

21 CFR	Item	Comment
	<p>(C) Reports previously not reported adverse drug experiences that occur in post approval studies must be reported separately from other experiences in the periodic drug experience report and clearly marked or highlighted.</p>	<p>Adverse drug events occurring in post approval studies are to be reported separately from other experiences in the periodic DER and clearly marked or highlighted. Does this mean on Form FDA 1932? If so, it would require considerable additional work, especially for the first 2 years after approval. Such information is already included in the study report submitted to ONADE. Duplicate reporting would add an absurdly burdensome new requirement. See also our comments on 514.80 (b)(4)(iii).</p>
<p>514.80(b)(5)(iii)(A)(1)</p>	<p><i>Distributor's Statement</i> (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 such as "manufactured for" or "marketed by".</p> <p>AHI REVISION:                      The name and address of the distributor must be preceded by an appropriate qualifying phrase <u>as permitted by 21 CFR 201.1</u> such as "manufactured for" or "marketed by".</p>	<p>AHI contends the permitted qualifying phrase should not be limited to 'manufactured for' or 'distributed by'. 21 CFR 201.1 provides the appropriate alternatives, which should also be permitted. The regulation should be changed to include this reference.</p> <p>Accordingly, AHI proposes that the last sentence in this section should be changed to read:                      The name and address of the distributor must be preceded by an appropriate qualifying phrase <u>as permitted by 21 CFR 201.1</u> such as "manufactured for" or "marketed by".</p>
<p>514.80(b)(5)(iii)(B)(2) &amp; (3)</p>	<p><i>Distributor's Statement. A signed statement by the distributor stating ...</i></p> <p>(2) that the distributor will distribute the new animal drug only under the approved labeling,</p>	<p>AHI notes that the current regulation [21 CFR 514.8(a)(6)(iii)] requires the distributor to state that he will promote 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. The new provisions appear to omit the limitation on promotional labeling as (3) only covers advertisements,</p>

21 CFR	Item	Comment
	<p>(3) that the distributor will advertise the product only for use under the conditions stated in the approved labeling,</p> <p>AHI REVISION:</p> <p>(2) that the distributor will distribute the new animal drug only under the approved labeling,</p> <p>(3) that the distributor will <u>promote</u> 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</p>	<p>which are not under CVM jurisdiction if the drug is OTC. Does CVM use the terms <i>promote</i> and <i>advertise</i> interchangeably in this context? If so, this would not be in accordance with the definitions in 21 CFR 202.1(k). AHI suggests that the language of 21 CFR 514.8(a)(6)(iii) be retained.</p>
514.80 (c)(4)	<p><i>Multiple Applications.</i> Whenever an applicant is required to submit a periodic drug experience report under the provisions of § 514.80(b)(4) with respect to more than one approved NADA or ANADA for preparations containing the same new animal drug so that the information is required to be reported for more than one application, the applicant may elect to submit as a part of the report for one such application (the primary application) all the information common to such applications in lieu of reporting separately and repetitively on each. If the applicant elects to do this, the applicant must do the following:</p> <p>...</p>	<p>AHI feels that, although well intentioned, the reporting requirements in this section do not appear to lessen the burden on applicants, because the sponsor must submit to the parent file and each referenced file. Unless FDA intends this to mean only additional copies of Form FDA 2301, not much is gained. Clarification from FDA is needed on (4) as to how many files are required when a combined report is submitted. This requirement could increase the reporting burden on the sponsor over current industry practices.</p> <p>We are also concerned that, with the enactment of the Animal Drug Availability Act of 1996, the number of approved combinations of drugs for use in feed has increased, thereby increasing the number of required reports. We would note that such NADAs frequently involve drugs of more than one sponsor, each of who may</p>

21 CFR	Item	Comment
	(4) All other information specific to a particular NADA/ANADA must be included in the report for that particular NADA/ANADA.	independently promote use of the combination. Except for promotional literature, there is rarely anything to report for the feed combination NADA. AHI sees no reason to make a separate report in this circumstance. Such information can be reported by the individual drug's sponsor (not necessarily the sponsor of the NADA for the combination) in the periodic drug experience for its Type A medicated article (in other words, a primary application).

AHI also recommends that CVM adopt a waiver procedure for reporting adverse drug experiences for animal drugs similar to one described in the Center for Drug Evaluation and Research's March 2001 draft publication, GUIDANCE FOR INDUSTRY. Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines. CDER will allow drug sponsors to request a waiver from submission of full adverse drug experience reports (postmarketing events only) that are determined to be both non-serious and labeled, if the sponsor commits to certain conditions.

We appreciate the opportunity to provide these comments and are available to answer any questions about them.

Sincerely yours,



Richard A. Carnevale