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Marketing and
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Programs

Animal and Plant
Health Inspection
Service

Veterinary Services

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CENTER FOR VETERINARY BIOLOGICS NOTICE NO. 01-11

Subject: International Cooperation on Harmonization of Technical Requirements for the Registration of Veterinary Medicinal Products (VICH): Final Guidelines for Good Clinical Practice

To: Biologics Licensees, Permittees, and Applicants
Directors, Center for Veterinary Biologics

I. PURPOSE

The purpose of this notice is to inform all interested parties of the disposition of the comments we received in response to the *Federal Register* notice of availability and request for comments on a draft guideline titled, "Good Clinical Practices" (VICH GL9) developed by the International Cooperation on Harmonization of Technical Requirements for Veterinary Medicinal Products (VICH).

Veterinary Services has issued the final guideline for Good Clinical Practice as Veterinary Services Memorandum 800.301, which accompanies this notice.

II. BACKGROUND

The guideline was published in the *Federal Register* (64 FR 34764, Docket No. 99-045-1) on June 29, 1999. Because the topic of the draft guideline concerns veterinary biological products, we requested comments on its provisions so that we could include any relevant input on the draft to the VICH for its consideration to support the expertise available to the working group preparing the final guideline.

III. COMMENTS AND DISPOSITION

We received four sets of comments on the draft guideline. One set of comments inquired if the guideline applied to *in vitro* diagnostic test kits, and provided some specific comments if the guideline were to be applied to these kits. By definition, clinical studies are "conducted in a target species," therefore, *in vitro* diagnostics are outside the scope of this guideline, and the specific comments were not addressed.

— some specific revisions to the draft guideline. These positions are as follows:



Section 1.1 (one comment): It was suggested that the definition of “adverse event” be revised to be compatible with that developed by the VICH 24 Working Group (Pharmacovigilance of Veterinary Medical Products: Management of Adverse Event Reports). We agree with this suggestion, and the guideline was revised to use their definition.

Section 1.17 (one comment): It was suggested that the definition of “Investigational Veterinary Product” be revised from “any pharmaceutical form” to “any biological or pharmaceutical form”. This change has been made.

Sections 1.26 and 4.1 (two comments each): It was suggested that “and is liable” be deleted from the definition of “Sponsor” in the phrase “takes responsibility and is liable”. These changes have been made.

Section 1.33 (one comment): It was suggested that “to effect physiological functions” should read “to affect physiological functions”. This change has been made.

Section 2.7 (three comments): It was suggested that the phrase “of the relevant regulatory authorities” be added after the phrase “good manufacturing practice” in the first sentence, due to the absence of a single, universally accepted definition of “Good Manufacturing Practice”, and in recognition of product made in accordance with the manufacturing practices required by the relevant regulatory authority. This change has been made.

Section 3.13 (one comment): It was suggested that an APHIS Form 2007 should be adequate to demonstrate evidence that the investigator has appropriate credentials for conducting studies. We agree that if the investigator is a permanent employee of the firm, an APHIS Form 2007 is adequate. No change was made to the document because it was agreed that this is an acceptable local interpretation.

Section 3.2.6 (one comment): It was suggested, and we agreed, that the sponsor should be notified “promptly” rather than “immediately” of the occurrence of study protocol deviations. The change has been made.

Section 3.2.13 (three comments): One commentator suggested that the word “must” be replaced with the word “should” in the sentence “...owner’s agent must receive relevant...”. We agree. The document is intended as a guideline, and is not a regulation. Therefore, the word “must” is inappropriate and has been changed to “should”. Two comments suggested that if the animal is owned by the sponsor, informed consent is unnecessary or implicit, and should not require documentation. We agree, but studies conducted using animals owned by a sponsor do not constitute clinical practice. Therefore, this guideline does not apply, and no further changes were made.

Section 4.2.7, 8.1.2, and 8.4.1 (one comment each): It was suggested that the word “must” be replaced with “should”. These changes have been made (see rationale explained in 3.2.13).

Section 4.2.11 (one comment): A request to clarify “final and safe disposal of all study animals” was made. We attempted to clarify the intent by stating that the sponsor should “Ensure the proper disposal of all study animals according to the applicable regulatory requirements.” We agree that most clinical studies will not require “final and safe disposal” of the study animals.

Section 5.1 (one comment): It was suggested that the monitor need not be trained in data auditing procedures. We agreed with the suggestion to delete the phrase, “and data auditing procedures.”

Section 5.2.7 (one comment): It was suggested that the phrase “bias or be a part of”, be deleted from the first sentence, “Not, in any way, bias or be a part of the record-keeping”. We agreed this sentence needed clarification, and the sentence was revised to read “Not, in any way, bias the data collection process or outcome of the study...”.

Section 6.3.20.1 (one comment): It was suggested that this section limit SOP’s to those specific to the technical conduct of the study. We agreed, and added the words “study-specific” to the sentence.

Section 7.3.6.4 (one comment): It was suggested that “complete description” be replaced with “summary” in the sentence “a complete description of the disposal...”. We agreed with the suggestion, and the change has been made.

Section 8.1.3 (one comment): It was suggested that this section be revised to include a statement to protect the sponsor’s confidential business information. We believe existing regulatory restrictions on the confidentiality of this information are sufficient. No changes were made.

In addition to the above comments suggesting substantive changes, several typographical errors were brought to our attention, and have been corrected.

IV. ADDITIONAL DISCUSSION

Two general comments indicated that the intent of the VICH guideline may not be well understood, and should be clarified. Publication of the guideline is not meant to imply that adherence to the document represents the only acceptable route to regulatory approval of a product. Rather, it provides product manufacturers with relative assurance that favorable data collected in accordance with the guidelines will be acceptable to all three regions participating in the VICH process.

The guidelines are meant to be applied only to *clinical studies*. APHIS interprets the term “clinical studies” to be those conducted in the context in which unlicensed product will be used in what the APHIS has usually referred to as “field safety” or “field efficacy” studies. The animals enrolled in these studies are client-owned animals, which are recruited by the

investigator(s) within a veterinarian-client-patient relationship, and data are typically collected from multiple sites.

The guideline does not apply to controlled studies conducted by companies or their contractors to support efficacy, safety, lack of reversion to virulence, etc. APHIS interprets the term “controlled studies” to be those conducted in a controlled environment, using animals that are owned by the manufacturer (or the contractor). These types of studies will be covered by other applicable guidelines at such time as they are developed. Interested parties will have the opportunity to comment on the documents prior to finalization and implementation.

The document is intended to be a comprehensive guideline for any and all types of clinical practice studies, and while some points may not be commonly applicable to most veterinary biologics studies, they may be an important consideration for others. For example, the information requested in 6.3.11 through 6.3.12, detailing animal management, housing, and feeds might not be relevant in a field safety trial for a conventional parenteral vaccine intended for use in feedlot cattle. In this case, a simple statement indicating that animals receive normal husbandry and care could be adequate. However, in a double-masked field efficacy study for a plant-derived veterinary biological, which is intended for prolonged oral administration to feedlot cattle, the information requested in these sections could be highly relevant. We do not intend to use this guideline as a protocol “check list”, nor will we require excessive documentation for information in sections of the guideline that are not relevant.

Finally, concerns were raised regarding access of the United States biologics industry to the VICH process. We believe these concerns were addressed when the VICH Steering Committee adopted criteria for the acceptance of “interested parties,” and granted this status to individuals or groups which met certain criteria. In addition, the VICH has initiated a program of public conferences, which provide an opportunity for the public to review progress and make comments on specific guidelines and on the VICH process in general.

/s/ James E. Tanner for

Richard E. Hill, Jr.
Director
Center for Veterinary Biologics

Enclosure