United States Department of Agriculture
Animal and Plant Health Inspection Service

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Inspection Report

Comparative Biosciences, Inc.
786 Lucerne Drive
Sunnyvale, CA 94085

Customer ID: **1761**
Certificate: **93-R-0398**
Site: 003
COMPARATIVE BIOSCIENCES, INC.

Type: ROUTINE INSPECTION
Date: 14-AUG-2017

2.31(c)(7)

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC).

Protocol 6004 involving a study of pigs with skin biopsy with weight range of 9-10 kg. It was approved by the IACUC as Category D on the Integrated Proposal form. However, the same form also indicated that buprenorphine was to be administered intramuscularly, but no other details were provided. The protocol indicated that analgesic use would be provided according to the standard operating procedure for analgesics (SOP ARL-EX-027). Review of the study records indicated that a custom-compounded, sustained-release buprenorphine formula was used. The SOP did not include any information related to this sustained-release formula, but did include the dose information for the standard commercially-available product, which was to be administered at a dose of 0.05-0.1 mg/kg twice daily.

The labels on the vials of the sustained release buprenorphine instructed it to be administered at a dose of 1.58 mL of the 1 mg/mL solution subcutaneously to be administered every 3 days post-biopsy (effective dose of 1.58 mg every three day). The subcutaneous route of administration was different than the approved protocol, which stated intramuscular administration. Further, calculation of the buprenorphine, based upon the dosage information within the SOP, indicated that insufficient buprenorphine was administered, e.g. a 9 kg pig at the lowest dose level would have required 2.7 mg in a three-day period.

Incomplete information regarding analgesic use included in the protocol could result in an incorrect dose, such as occurred in protocol 6004, and therefore inadequate pain relief. The change in buprenorphine formulation might have affected the degree of analgesia provided.

Any proposal to use animals or any significant modifications to such proposals must contain a complete description of such activities and must be approved by the IACUC.

The noncompliance cited above should be corrected for all future proposals as well as the referenced protocol, if it is to be continued to be used.

2.31(d)(1)(iv)(A) **REPEAT**

Prepared By: SCHNELL MICHAEL, D V M USDA, APHIS, Animal Care **Date:** 24-JAN-2018

Title: VETERINARY MEDICAL OFFICER 6100

Received by Title: SENT VIA EMAIL **Date:** 24-JAN-2018

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC).

Approved protocol proposal CB-I-9214 involving rabbits was reclassified as a Category E study. The IACUC chair issued a memo to the IACUC members on February 14, 2017 stating that, following the August 2016 USDA inspection, some changes have been made to some approved protocols. Protocol CB-I-9214 is now listed as a Category E protocol (changed from Category D). Category E studies are those where measures that would commonly be undertaken to minimize pain and distress, such as administering analgesics, cannot be undertaken because they would interfere with the goals of the study, and in order to be approved Category E study proposals must include such a scientific justification. Without an explanation as to why pain medications cannot be administered, the proposal should not be approved. The IACUC must ensure that the investigator has carefully considered all possible means to minimize any possible pain and/or distress. Although the pain category designation has changed for protocol CB-I-9214, no scientific justification has been added to this protocol.

The IACUC must ensure that no animals unnecessarily forego standard treatments to minimize pain and distress. No activities that might cause pain or distress in Category E studies should be conducted until the IACUC reviews such scientific justifications and approves such activities.

2.31(e)(4) **REPEAT**

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC).

Approved proposal CB-I-9242 involving rabbits is a Category E study. The proposal form included a section for “Other potential stressors and procedures to monitor and minimize distress," and the investigator stated: “Rabbits showing indication of pain or distress may be administered any of the following as relevant: systemic analgesics (e.g.: buprenorphine); topical local anesthetics.” Later in the “Justification for Classification E” section the investigator states: “… in most studies some toxicity will be intentionally produced and there may be attendant pain and/or distress, and even mortality. In general it is assumed that pain-relieving drugs may interfere with the toxicity to be observed, and such drugs are withheld.” Due to the conflicting details within the protocol, it is not clear whether there is any reason why these animals cannot receive pain medications. This protocol was previously cited for this reason and was uncorrected at the time of the inspection.

Protocol CB17-6030 involved application of a test article to the eye of pigs and subsequent evaluation of the resulting test article levels in the eye. It was approved by the IACUC as Category D, which the Integrated Proposal form indicated as “Are the procedures expected to cause more than minor distress, discomfort or pain but may be alleviated with the use of appropriate analgesics, anesthetics and/or tranquilizing drugs?” However, the same form also indicated that no analgesics were planned to be used. The protocol did not contain any further details about analgesics. The protocol also contained a table entitled “Modified Hackett-McDonald Ocular Scoring (Bilateral Measurements)” for the evaluation of corneal changes such as fluorescein staining. Certain corneal changes, such as a corneal ulcer, would be anticipated to be painful were they to occur and therefore would require appropriate analgesics.

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The IACUC must assure that all protocols contain a complete description of all procedures to be used, either directly or by reference prior to approval. Further as part of the protocol review process, the IACUC must review any other documents incorporated by reference to assure the appropriate care and use of animals. The protocol must be amended to contain information regarding appropriate analgesia prior to any future use.

This inspection and exit briefing were conducted with facility representatives.

Additional Inspectors

Theodorson Elizabeth, Director

Garland Kathleen, Supervisory Animal Care Specialist

Smith Pamela, Veterinary Medical Officer

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Species Inspected

Cust No	Cert No	Site	Site Name	Inspection
1761	93-R-0398	003	COMPARATIVE BIOSCIENCES, INC.	14-AUG-17

No Animals were Inspected.

Count	Scientific Name	Common Name
000000	NONE	NONE
000000	Total	