March 7, 2023

Calcivis Limited
% Ms. Angela Blackwell
Senior Consultant
Blackwell Device Consulting
P.O. Box 718
Gresham, OR 97030-0172

Re: P170029
Trade/Device Name: CALCIVIS Imaging System
Product Code: QJX
Filed: October 2, 2017
Amended: May 31, 2018; September 19, 2018; March 27, 2019; September 3, 2019; May 29, 2020; and February 21, 2023

Dear Ms. Blackwell:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the CALCIVIS Imaging System. The CALCIVIS Imaging System is intended to be used by dental healthcare professionals on patients (6 years and older) with, or at risk of developing, demineralization associated with caries lesions, on accessible coronal tooth surfaces. The CALCIVIS Imaging System is indicated for use to provide images of active demineralization on tooth surfaces, as an aid to the assessment, diagnosis and treatment planning of demineralization associated with caries lesions.

We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below. Although this letter refers to your product as a device, please be aware that some approved products may instead be combination products. The Premarket Approval Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm identifies combination product submissions.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Continued approval of the PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. This report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the PMA device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

You have agreed to provide the following non-clinical information in a non-clinical post-approval study report (or as part of the annual report for the identified Chemistry Manufacturing Control (CMC) request #2.a. below), which may be followed by a PMA supplement where applicable.

1. Please address the following as non-clinical post-approval requirements for assessment of the microbial control and microbiology product quality:

    a. Provide in-process data from three batches for the end of fermentation culture purity IPC 8 samples.

    b. Provide data to demonstrate the effect of kanamycin removal from the production culture media. Provide the report, summary of the study and the results, and the methods used to analyze the data. If the data support removal of kanamycin, submit a plan for the removal of kanamycin from the photoprotein manufacturing process.

    c. Provide in-process and release data for the bioburden test and release data for the absence of specified organisms test obtained from two additional drug substance and drug product lots.

    d. Provide qualification data from in-process and release samples for the bioburden method and from release samples for the specified microorganism detection method using samples from two additional lots.

    e. Provide summary data and the study report for the antimicrobial effectiveness study conducted according to USP <51> using photoprotein DP reconstituted in a commercial batch of diluent, which is at the end of the shelf life.

2. Please address the following as non-clinical post-approval requirements for assessment of the Chemistry Manufacturing Control (CMC) product quality:

    a. Revised the release and stability specification acceptance criteria for protein content by UV absorbance at 280 nm based on the protein content determination using experimental instead of theoretical extinction coefficient.

Protein content testing performed at different steps of drug substance (DS) and drug product (DP) manufacturing process was determined using the theoretical extinction coefficient. In order to meaningfully correlate the results from different steps and specification acceptance criteria (in-process control, DS and DP), revise the protein content values and acceptance criteria throughout the PMA documentation based on the experimental extinction coefficient. You may provide this information as part of the PMA annual report, instead of a non-clinical post-approval study report.

b. Develop and validate an assay that is suitable for accurately and reliably monitoring impurities in photoprotein Formulated Bulk Drug Product (FBDP) and Final Container Drug Product (FCDP) at release and on stability. Establish appropriate specification acceptance criteria for levels of impurities and implement the analytical method for testing impurities in FBDP and FCDP at release and on stability. The final study report for method validation will be submitted in accordance with 21 CFR 601.12.

c. Develop and validate an assay that is suitable for accurately and reliably monitoring host cell protein (HCP) in the photoprotein drug substance (DS). Establish appropriate specification acceptance criteria for HCP level and implement HCP testing by revising the current DS release specification. The final study report for method validation will be submitted in accordance with 21 CFR 601.12.

    i. For additional considerations of this request, you indicated that you plan to use commercial ELISA kit for detection of *E.coli* host cell proteins (HCP). The anti-*E.coli* HCP antibodies need to be qualified for their ability to detect potential HCP impurities. Provide data demonstrating that the anti- *E.coli* HCP antibodies employed can detect the majority of proteins present in an *E.coli* cell extract. These data should include 2D SDS-PAGE gels of the range of HCPs detected by a sensitive protein stain, such as silver stain, compared to the range detected by Western Blot analysis using the antibody employed in the ELISA. It is possible to use a similarly sensitive and discriminating assay instead of the 2D SDS-PAGE assay. If an alternative pathway is pursued, consultation with the Agency is recommended. These data should be used to determine the approximate percent of potential HCP impurities that are recognized by the HCP antiserum. It is the Agency's experience that analysis of HCP coverage by a 1-dimensional SDS-PAGE gel method is not sufficiently informative for this purpose.

Be advised that failure to comply with any post-approval requirement, including the non-clinical information outlined above, constitutes grounds for FDA withdrawal of approval of the PMA in accordance with 21 CFR 814.82(c) and 814.46(a)(2).

This is a reminder that as of September 24, 2014, class III devices are subject to certain provisions of the final Unique Device Identification (UDI) rule. These provisions include the requirement to provide a UDI on the device label and packages (21 CFR 801.20), format dates on the device label in accordance with 21 CFR 801.18, and submit data to the Global Unique Device Identification Database (GUDID) (21 CFR 830 Subpart E). Additionally, 21 CFR 814.84 (b)(4) requires PMA annual reports submitted after September 24, 2014, to identify each device identifier currently in use for the subject device, and the device identifiers for devices that have been discontinued since the previous periodic report.

It is not necessary to identify any device identifier discontinued prior to December 23, 2013. Combination Products may also be subject to UDI requirements (see 21 CFR 801.30). For more information on these requirements, please see the UDI website, https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/unique-device-identification-udi-system.

Before making any change affecting the safety or effectiveness of the PMA device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" https://www.fda.gov/media/81431/download.

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52 for devices or post-marketing safety reporting (21 CFR 4, Subpart B) for combination products, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems and on combination product post-marketing safety reporting is available at https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products.

In accordance with the recall requirements specified in 21 CFR 806.10 for devices or the post-marketing safety reporting requirements (21 CFR 4, Subpart B) for combination products, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/industry-guidance-recalls.

CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet Home Page located at https://www.fda.gov/medical-devices/device-approvals-denials-and-clearances/pma-approvals.

Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with a copy of all final labeling. Final labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final labeling is identical to the labeling approved in draft form. If the final labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning this approval order, please contact Joel Anderson at 301-796-6520 or Joel.Anderson@fda.hhs.gov.

Sincerely,

Malvina B. Eydelman -S

Digitally signed by Malvina B. Eydelman -S
Date: 2023.03.07 12:16:18 -05'00'

Malvina B. Eydelman, M.D.
Director
OHT1: Office of Ophthalmic, Anesthesia, Respiratory, ENT and Dental Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health