

APPROVAL ORDER



APR - 7 2004

Amy J. LaForte, Ph.D.
Director, Regulatory Affairs
Stryker Biotech
35 South Street
Hopkinton, Massachusetts 01748

Re: H020008
OP-1 Putty
Filed: August 18, 2003

Dear Dr. LaForte:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your humanitarian device exemption (HDE) application for the OP-1 Putty. This device is indicated for use as an alternative to autograft in compromised patients requiring revision posterolateral (intertransverse) lumbar spinal fusion, for whom autologous bone and bone marrow harvest are not feasible or are not expected to promote fusion. Examples of compromising factors include osteoporosis, smoking and diabetes. CDRH is pleased to inform you that your HDE is approved subject to the enclosed "Conditions of Approval." You may begin commercial distribution of the device after you have submitted an amendment to this HDE with copies of the approved labeling in final printed form.

In addition to the postapproval requirements in the enclosure, you have agreed to provide:

1. a continuation of the activities that were a condition of approval for H010002, specifically:
 - a. a preclinical plan for assessing the effects of OP-1 on tumor promotion;
 - b. a preclinical plan to investigate the potential for an immune response to OP-1 to interfere in embryonic development; and
 - c. a plan for addressing the preclinical and clinical immunological commitments; and
2. responses to the following deficiencies related to the test reports describing validation of a new, more sensitive ELISA for detecting rhOP-1 antibodies and validation of an ELISA for detecting rhOP-1 neutralizing antibodies:
 - a. Please provide data justifying a minimum required dilution of 1:80.

- b. Please provide statistical justification for the establishment of acceptability criteria (%CV) for each of the assay validation parameters.
- c. We are concerned that the method of determining assay cut point as well as the criteria for determining a positive antibody response is not appropriate. The selection and validation of a cutpoint are critical as the cutpoint is used to judge whether an immune response to the drug has occurred and therefore warrants significant scientific consideration.

We recommend establishing the cutpoint using a statistically-based method. For example, antibody-negative sera from approximately 50-100 normal individuals. Once the standard deviation of the mean is established, the 95% confidence limit should be identified. A positive serum sample would be one with a value higher than the 95% confidence limit value.

A negative control may be either a single or pooled serum sample that has a value approximating the mean for the assay.

- d. The false positive rate of 0.5% is low. We recommend that screening assays have a false positive rate of ~5%.
- e. The sensitivity of your binding assay is not reported. The limit of detection and the limit of quantitation should be demonstrated.
- f. On page 66 of the submission, you note considerable variability in normal human sera spiked with OP-1. Please explain the experiment performed here and what you are measuring.
- g. You propose a 50% inhibition of OP-1 activity when comparing a subject's pre- to post-treatment serum to define a positive neutralizing antibody response. The basis for this determination seems to be the variability seen in normal sera. Please provide a statistically based justification for determining a true immune response to OP-1. We recommend that you determine a confidence interval for the reproducibility of the assay using individual negative and positive serum samples. Then, once a statistically-justified confidence interval is established (eg. 80%), one can justify that the difference between a predose antibody level and levels post-dose represent a true difference due to exposure to OP-1 and is not due to assay variability. This avoids the arbitrary 50% decrease you proposed, and will most likely decrease the number of false negatives.
- h. Please provide the appendices mentioned regarding assay validation data but not included in the submission (as an example, see page 57, Table 1).

- i. Please provide more supporting data for the validation studies performed for your binding and neutralizing ELISAs. Please include standard curves illustrating assay linearity.
- j. Your neutralizing assay was only validated for stimulatory parameters, namely OP-1. You also need to validate the sensitivity of the assay to inhibition using anti-OP-1 antibodies.
- k. In your neutralizing assay validation studies, please include the expected values, as well as the values obtained experimentally. For example, in Table 5 on page 68, your mean concentration of OP-1 positive control was about 20 ng/mL. How much was added to the plate initially?
- l. Please submit the data from the neutralizing ELISA using positive samples from the tibial nonunion study as they become available.

The sale, distribution, and use of this device are limited to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. In addition, in order to ensure the safe use of the device, FDA has further restricted the device within the meaning of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

In addition to the above, an FDA inspection must find that your manufacturing facilities, methods, and controls for this device comply with the applicable Current Good Manufacturing Practice requirement, as set forth in the Quality System Regulation (QS) for Medical Devices; General regulation (21 CFR Part 820). Such an inspection will be scheduled and conducted by your District Office. If you have any questions regarding the status of your GMP inspection, please contact your District Office or the Office of Compliance, CDRH at (301) 594-4695.

FDA wishes to remind you that failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

CDRH will notify the public of its decision to approve your HDE by making available a summary of the safety and probable benefit of the device upon which the approval was based. The information can be found on the FDA CDRH Internet HomePage located at <http://www.fda.gov/cdrh/ode/hdeinfo.html>. Written requests for this information can also be made to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the HDE 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 requesting an opportunity for administrative

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review, either through a hearing or review by an independent advisory committee, under section 515(g) of the act.

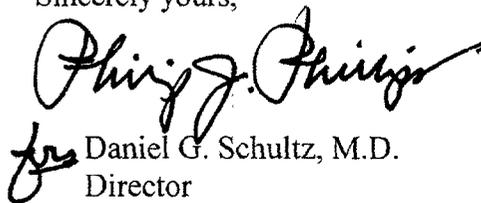
You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this HDE submission with copies of all approved labeling in final printed form. As part of our reengineering effort, the Office of Device Evaluation is piloting a new process for review of final printed labeling. The labeling will not routinely be reviewed by FDA staff when HDE applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment. Please see the CDRH Pilot for Review of Final Printed Labeling document at <http://www.fda.gov/cdrh/pmat/pilotpmat.html> for further details.

Any information to be submitted to FDA regarding this HDE should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above HDE number to facilitate processing:

Document Mail Center (HFZ-401)
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Mr. Aric D. Kaiser at (301) 594-2036.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Daniel G. Schultz, M.D.", with a stylized flourish at the end.

Daniel G. Schultz, M.D.
Director
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

CONDITIONS OF APPROVAL FOR AN HDE

I. APPROVED LABELING

As soon as possible and before commercial distribution of the device, the holder of an HDE should submit three copies of the approved labeling in final printed form as an amendment to the HDE. The supplement should be submitted to the Document Mail Center (HFZ-401), Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

II. ADVERTISEMENTS

Advertisements and other descriptive printed materials issued by the HDE holder or private label distributor with respect to this device should not recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360j(e)) under the authority of section 515(d)(1)(B)(ii) of the act (21 U.S.C. 360e(d)(1)(B)(ii)), all advertisements and other descriptive printed material issued by the holder or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects, and contraindications.

III. HDE SUPPLEMENTS

Before making any change affecting the safety or probable benefit of the device, the HDE holder should submit a supplement for review and approval by FDA unless a "Special HDE Supplement" is permitted as described under 21 CFR 814.39(d)(2) or an alternate submission is permitted as described under 21 CFR 814.39(e). All HDE supplements or alternate submissions must comply with the applicable requirements under 21 CFR 814.39 of the Premarket Approval (PMA) regulation and under 21 CFR 814.108 of the Humanitarian Device Exemption regulation. The review timeframe for HDE supplements is 75 days except for those submitted under 21 CFR 814.39(e).

Since all situations which require an HDE supplement cannot be briefly summarized, please consult the HDE regulation for further guidance. The guidance provided below is only for several key instances. In general, an HDE supplement must be submitted:

- 1) When unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification; or
- 2) If the device is to be modified, and animal/laboratory or clinical testing is needed to determine if the modified device remains safe and continues to provide probable benefit.

HDE supplements submitted under 21 CFR 814.39(d)(2) "Special HDE Supplement - Changes Being Effected" are limited to the labeling, quality control, and manufacturing process changes as specified under this section of the regulation. This provision allows for the addition of, but

not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented upon acknowledgment by FDA that the submission is being processed as a "Special HDE Supplement - Changes Being Effected." Please note that this acknowledgment is in addition to that issued by the Document Mail Center for all HDE supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software, or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of an HDE supplement before implementation and include the use of a *30-day HDE supplement* or *periodic postapproval report*. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence to the HDE holder that the alternate submission is permitted for the change. Before this can occur, FDA and the HDE holder must agree upon any needed testing, the testing protocol, the test results, the reporting format, the information to be reported, and the alternate submission to be used.

Please note that unlike the PMA process, a supplement may not be submitted for a new indication for use for a humanitarian use device (HUD). An HDE holder seeking a new indication for use for an HUD approved under the provisions of Subpart H of 21 CFR 814, must obtain a new designation of HUD status for the new indication for use and submit an original HDE application in accordance with §814.104. The application for the new indication for use may incorporate by reference any information or data previously submitted to the agency.

IV. POSTAPPROVAL RECORD KEEPING REQUIREMENTS

An HDE holder is required to maintain records of the names and addresses of the facilities to which the HUD has been shipped, correspondence with reviewing institutional review boards (IRBs), as well as any other information requested by a reviewing IRB or FDA.

V. POSTAPPROVAL REPORTING REQUIREMENTS Continued approval of the HDE is contingent upon the submission of postapproval reports required under 21 CFR 814.84 and 21 CFR 814.126.

A. ANNUAL REPORT

Annual reports should be submitted at intervals of 1 year from the date of approval of the original HDE. Reports for supplements approved under the original HDE should be included in the next and subsequent periodic reports for the original HDE unless otherwise specified in the approval order for the HDE supplement. Three copies identified as "Annual Report" and bearing the applicable HDE reference number are to be submitted to the HDE Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. Reports should indicate the beginning and ending date of the period covered by the report and include the following information required by 21 CFR 814.126(b)(1):

1. An update of the information required under §814.102(a) in a separately bound volume;
2. An update of the information required under §814.104(b)(2), (b)(3), and (b)(5);
3. The number of devices that have been shipped or sold and, if the number shipped or sold exceeds 4,000, an explanation and estimate of the number of devices used per patient. If a single device is used on multiple patients, an estimate of the number of patients treated or diagnosed using the device together with an explanation of the basis for the estimate;
4. Information describing the applicant's clinical experience with the device. This shall include safety information that is known or reasonably should be known to the applicant, a summary of medical device reports made pursuant to 21 CFR 803, any data generated from postmarketing studies, and information (whether published or unpublished) that is known or reasonably expected to be known by the applicant that may affect an evaluation of the safety of the device or that may affect the statement of contraindications, warnings, precautions, and adverse reactions in the device labeling; and
5. A summary of any changes made to the device in accordance with supplements submitted under §814.108 and any changes required to be reported to FDA under §814.39(b).

B. ADVERSE REACTION AND DEVICE DEFECT REPORTING

As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and probable benefit of the device, the holder shall submit three copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the Document Mail Center (HFZ-401), Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. Such reports should be submitted within 10 days after the HDE holder receives or has knowledge of information concerning:

- (1) A mixup of the device or its labeling with another article.
- (2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and
 - (a) has not been addressed by the device's labeling or
 - (b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.
- (3) Any significant chemical, physical or other change or deterioration in the device or

any failure of the device to meet the specifications established in the approved HDE that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the HDE holder's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the firm. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the holder shall be included in the "Annual Report" described under "Postapproval Reports" above unless otherwise specified in the conditions of approval for this HDE. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of occurrence for each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the HDE holder when determined by FDA to be necessary to provide continued reasonable assurance of the safety and probable benefit of the device for its intended use.

C. **REPORTING UNDER THE MEDICAL DEVICE REPORTING REGULATION**

The Medical Device Reporting regulation (MDR) (21 CFR 803) became effective on July 31, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise become aware of information that reasonably suggests that one of its marketed devices:

- (1) may have caused or contributed to a death or serious injury; or
- (2) has malfunctioned and that the device or a similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Events subject to reporting under the MDR regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements. FDA has determined, however, that such duplicative reporting is unnecessary. Therefore, whenever an event involving a device is subject to reporting under both the MDR regulation and the "Adverse Reaction and Device Defect Reporting" requirements, the report should be submitted in compliance with Part 803 and identified with the HDE reference number to Food and Drug Administration, Center for Devices and Radiological Health, Medical Device Reporting, PO Box 3002, Rockville, Maryland 20847-3002. If you have MDR regulation questions, please send an e-mail to RSMB@CDRH.FDA.GOV or call (301) 594-2735.

Events included in periodic reports to the HDE that have also been reported under the MDR regulation must be so identified in the periodic report to the HDE to prevent duplicative entry into FDA information systems.

Copies of the MDR regulation and FDA publications, entitled "An Overview of the Medical Device Reporting Regulation" and "Medical Device Reporting for Manufacturers," are

available on the CDRH WWW Home Page (<http://www.fda.gov/cdrh>), through CDRH's Fact-on-Demand (FOD) at 800-899-0381 (FOD # 336, 1336, 509 and 987) or by written request to the address below or by telephoning 1-800-638-2041.

Division of Small Manufacturers International
and Consumer Assistance (HFZ-220)
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive
Rockville, Maryland 20850