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JUN 19 2001

Food and Drug Administration  
Center for Devices and  
Radiological Health  
2098 Gaither Road  
Rockville, MD 20850

**WARNING LETTER**

**VIA FEDERAL EXPRESS**

**VIA FACSIMILE**

Dr. Patricia Young, Ph.D.  
Vice-President, Regulatory Affairs  
Sanofi-Synthelabo, Incorporated  
90 Park Avenue  
New York, New York 10016

Re: Hyalgan (Sodium Hyaluronate  
Injection), P950027

Dear Dr. Young:

The Office of Compliance (OC), Center for Devices and Radiological Health (CDRH), Food and Drug Administration (FDA) has reviewed promotional materials for Hyalgan (Sodium Hyaluronate Injection) (Hyalgan). This product is manufactured by FIDIA S.p.A., Padua, Italy (FIDIA), distributed in the United States by Sanofi-Synthelabo, Incorporated (Sanofi), and is a device within the meaning of section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

Hyalgan was approved through the Premarket Approval process (PMA) pursuant to section 515(d)(1)(B)(ii) of the Act and is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy, and to simple analgesics, e.g., acetaminophen. Hyalgan's overall success for effectiveness was studied for up to 26 weeks.

As you may recall, agency representatives met with Sanofi, FIDIA, and Orthologic representatives on June 29, 2000 to discuss several promotional issues concerning Hyalgan. Some of the issues raised by the agency included the promotion of Hyalgan for a 3-injection course of therapy; references to the absence of chemical cross-linkage with formaldehyde, implications that Hyalgan was effective for longer than 26 weeks, and Sanofi's failure to fully comply with the requirements under 21 CFR 801.109(d) and with section 502(r) of the Act.

We have come into possession of several Sanofi advertisements for Hyalgan that appeared in the March/April 2001 issue of the *Journal of the American Academy of Orthopedic Surgeons*, and the April 2001 issues of the *Journal of Bone and Joint Surgery*, *The American Journal of*

*Orthopedics, and the American Academy of Orthopedic Surgeons Bulletin.*

These materials make the following claims:

-“Now in a 3-injection regimen...”

-“Hyalgan contains a natural, highly purified hyaluronate that is not chemically cross-linked”

-“The only hyaluronate with NO inflammatory reactions.”

-“Hyalgan itself has not been shown in published studies to cause severe acute inflammatory reactions, unlike cross-linked hyaluronate.”

-In a 30-month study, no serious or local systemic side effects were observed despite long-term repeated use.”

The claim regarding the 3-injection regimen is misleading because Hyalgan is still only approved for a 5-injection regimen. Although the approved labeling indicates that some patients may experience benefit after 3 injections, Sanofi may not imply that a 3-injection course is currently approved. We note that one of your advertisements correctly states that patients treated with a 3-injection treatment course were followed for 60 days; however, your other advertisements do not include this caveat. If Sanofi wishes to refer to a 3-injection regimen, the company must qualify the claim with the additional statements in the approved labeling Directions for Use: “Some patients may experience benefit with three injections given at weekly intervals. This has been noted in studies reported in the literature in which patients treated with three injections were followed for 60 days.” The statement must appear on the same page and in type font that is easily readable.

As previously noted, Hyalgan’s effectiveness has only been proven for a period of up to 26 weeks. Sanofi’s references to a 30-month study and to “long-term repeated use” implies a change in the effectiveness of the device. Similarly, a claim for a 3-injection course of therapy changes the effectiveness of the device. The regulations under 21 CFR 814.39 provide that an applicant shall submit a PMA supplement for review and approval by the agency before making a change affecting the safety or effectiveness of the device. Changes, for which an applicant shall submit a PMA supplement include, but are not limited to, new indications for use of the device and labeling changes.

Claims that Hyalgan is approved for a 3-injection regimen and/or statements which state or imply that Hyalgan is effective beyond 26 weeks causes your device to be misbranded within the meaning of section 502(o) of the Act, in that a notice or other information respecting the modification in the intended use of the device was not provided to FDA as required by section

510(k) of the Act, and the device was not found to be substantially equivalent to a predicate device.

Hyalgan is also adulterated within the meaning of section 501(f)(1)(B) of the Act in that it is a Class III device under section 513(f), and does not have an approved PMA in effect pursuant to section 515(a), or an approved application for investigational device exemption under section 520(g).

This letter is not intended to be an all-inclusive list of deficiencies associated with your Hyalgan device. It is your responsibility to ensure adherence to each requirement of the Act and Federal regulations. The specific violations noted in this letter may represent practices used in other promotion or advertising materials used by your firm. You are responsible for investigating and reviewing these materials to assure compliance with applicable regulations.

You should take prompt action to correct these violations. Failure to promptly correct these deviations may result in regulatory action being initiated by FDA without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil penalties.

Please notify this office, in writing, within 15 working days of receipt of this letter, outlining the specific steps you have taken to correct the cited violations. Your response should also include all steps being taken to address misleading information currently in the market place and actions to prevent similar violations in the future. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

In addition to the violative claims, the advertisement raises some other concerns. The agency cannot agree to the company's use of continued references highlighting the absence of chemical cross-linkage. Chemical cross-linkage with formaldehyde is part of the manufacturing process of a competitor product. The Office of Device Evaluation has informed us, however, that most of the formaldehyde is removed in the manufacturing process and any remaining amount of formaldehyde and/or cross-linkage is insignificant. We believe Sanofi's statement that Hyalgan is not chemically cross-linked implies that your competitor's product is unsafe. The agency has made no such determination. Additionally, at the June 29<sup>th</sup> meeting, you agreed not to make references to formaldehyde in your promotional materials.

Also, claims that Hyalgan is the only hyaluronate without inflammatory reactions are untrue. The Adverse Events section of the approved labeling includes several reports of inflammatory reactions such as: knee swelling/effusion, local skin reactions (rash, ecchymosis), pruritis, two cases of anaphylactoid reactions, and three cases of allergic reactions.

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Please submit your response to Mr. Steven E. Budabin, Consumer Safety Officer, Promotion and Advertising Policy Staff (HFZ-302), Office of Compliance, Center for Devices and Radiological Health, 2098 Gaither Road, Rockville, Maryland 20850.

A copy of this letter is being sent to FDA's New York District Office. Please send a copy of your response to the District Director, Food and Drug Administration, New York District Office (HFR-NE100), 158-15 Liberty Avenue, Jamaica, New York 11433.

Sincerely yours,

  
for Larry D. Spears  
Acting Director  
Office of Compliance  
Center for Devices and  
Radiological Health

cc:  
Gordon Proctor  
CEO