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FISONS' OPTICROM, IMFERON MAY BE OFF U.S. MARKET UNTIL LATE 1992 AS THE COMPANY UPGRADES U.K. MANUFACTURING PLANT TO MEET FDA QUALITY CONTROL CONCERNS

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Executive Summary

Fisons' Opticrom (cromolyn sodium) eye drops and Imferon injectable iron are unlikely to be reintroduced in the U.S. until the second half of 1992 while the company deals with quality control problems turned up in a series of recent FDA inspections, Fisons reported Dec. 11. Reintroductions of the two products during the second half of next year would mean the company would have taken two years to resolve regulatory problems with the products. Fisons issued Class I and Class II recalls of Opticrom anti-allergic prescription eye drops and a Class III recall of Imferon in July 1990. Opticrom has been unavailable in the U.S. since the recall and Imferon has not been in supply since May 1991. Fisons is hoping to bring the two products back to market after an anticipated FDA inspection of the company's upgraded U.K.-based manufacturing facility in the first quarter of 1992. The firm does not expect "full normality" to be restored until the end of the year, the company said. FDA has inspected the Fisons plant in Holmes Chapel, England three times since February 1990, most recently in November. The first inspection revealed "significant drug CGMP [current good manufacturing practices] deviations" for three Fisons products sold in the U.S.: Opticrom, Imferon and the Intal inhaler, the FDA investigators noted in their report. [Emphasis added by FDA.] The FDA investigators listed a total of 30 "objectionable conditions" observed during the February 1990 inspection. Fisons' problems with Opticrom dated back to mid-1989, FDA discovered, when the company experienced over 100 positive sterility tests over a three-month period. Fisons attributed all but one positive test to lab contamination, FDA said, despite positive results from a second testing lab. FDA objected to the absence of an adequate investigation into the source of the contaminant and speculated that it was most likely "product contamination originating with the water system," which had "several significant discrepancies." Among the 11 objections cited for Imferon injection were: the iron dextran active ingredient was not tested for purity prior to use in the batch formulation; the "pyrogen-free" water system was deficient; empty bulk solution transport vessels were stored outside with open covers; filtered Imferon solutions were being stored in beer kegs that were

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considered "not of pharmaceutical quality"; and the firm did not perform visible particulate evaluations on each lot manufactured. Intal inhalers have had aerosol leakage problems since early 1987, FDA reported, and Fisons changed the valve design without obtaining prior NDA approval. FDA found that the valve change was not an improvement, but that the "new valve was reported as cheaper than the old valve." The inspectors also criticized Fisons' "deceptive" aerosol leakage tests, which eliminated low- weight inhalers from testing even though they may have been low weight due to aerosol leakage. In response to the violations cited by FDA, Fisons requested a second inspection in May 1991. FDA found that the company "had not made substantial corrections to the previously observed GMP deviations" for the manufacture of Imferon. The inspectors also concluded that "the firm's reported corrections to eliminate aerosol leakage [for the Intal inhaler] have not corrected the defect." Both Opticrom and Imferon, which are manufactured exclusively in the U.K., "remain on the import alert list," FDA noted in its inspection report. The Intal inhaler was apparently allowed to stay on the market in the U.S. due to a decision by FDA based on the "medical necessity of the product." Fisons subsequently decided to do "a more comprehensive overhaul" of the Holmes Chapel facility to meet FDA requirements, the company said. The third inspection in November 1991 was limited to the Imferon manufacturing process, which will apparently require further improvements before receiving FDA approval. Fisons also has submitted a supplemental NDA for a new Intal inhaler valve manufactured by Vespec, the firm said. Opticrom has not been produced at the Holmes Chapel plant since November 1990 when British health authorities revoked the company's license to manufacture and release sterile products. The license revocation letter stated: "'The levels of quality assurance of sterile products as demonstrated by end product, and in-process microbiological testing are not of an acceptable standard,'" according to the FDA report. The license has not yet been reinstated, the company said. Fisons estimates that the withdrawal of Opticrom and Imferon from the U.S. market will result in "a loss of profit of some (BRITISH POUND)33 mil.," or around $ 60 mil. in 1991. Additional costs include an estimated $ 36 mil. as a result of "the disruption caused to production activities arising from upgrading at the main U.K. plant to supply the U.S. market." The disruption in the supply of Opticrom to other markets is costing the firm around $ 27 mil. ((BRITISH POUND)15 mil.), with the "total impact on profits" amounting to approximately $ 117 mil. ((BRITISH POUND)65 mil.), Fisons reported. In response to what it described as "increasingly stringent standards set by the U.S. FDA," Fisons also has appointed a new divisional technical director as well as 71 new managers in the area of "technical management and quality control" for the pharmaceutical division, the company said.