received on the November 19, 1986, final rule, and modified the rule in response to some of the objections. The major changes to the final rule that the agency made included extending the effective date of the labeling requirement to January 1, 1989, and modifying the language of the labeling requirement.

On October 5, 1987, the Certified Color Manufacturers Association (CCMA, now the International Association of Color Manufacturers) filed a petition in the United States Court of Appeals for the District of Columbia Circuit challenging that portion of the final rule that required that food labeling declare the presence of FD&C Yellow No. 6. The issues raised by CCMA were: (1) Whether FDA provided sufficient notice under the provisions of the Federal Food, Drug, and Cosmetic Act (the act), FDA regulations, the Administrative Procedure Act, and the Due Process Clause of the United States Constitution of its intent to adopt this requirement; and (2) whether this requirement is supported by the evidence.

On February 29, 1988, CCMA and FDA presented the Court of Appeals with a stipulation for the voluntary dismissal of the petition. In the stipulation, FDA agreed to ''issue a **Federal Register** notice withdrawing, as a final rule, the labeling requirement set forth at 52 FR 21505, June 8, 1987, and simultaneously publish as a proposed rule a labeling requirement for FD&C Yellow No. 6.'' This agreement did not affect the permanent listing of the color additive.

The agency never published a notice of withdrawal for the labeling requirement set forth in 1987 (52 FR 21505), but in the **Federal Register** of December 6, 1988 (53 FR 49138), the agency published a notice that stated that the labeling requirements for FD&C Yellow No. 6 would not be enforced until further notice.

In November of 1990, Congress passed, and the President signed, the Nutrition Labeling and Education Act (the 1990 amendments). The 1990 amendments amended section 403(i) of the act (21 U.S.C. 343(i)) to require the listing by name, as part of the list of ingredients, of color additives that are subject to certification under section 721(c) of the act (21 U.S.C. 379e(c)) (section 7 of the 1990 amendments). However, the 1990 amendments did not change section 403(k) of the act, which continues to provide that section 403(i) of the act, with respect to artificial coloring, does not apply in the case of butter, cheese, or ice cream.

In response to the 1990 amendments, FDA adopted § 101.22(k) (21 CFR 101.22(k)), which became effective on May 8, 1993. Section 101.22(k)(1) requires the label declaration of certifiable color additives added to foods, while § 101.22(k)(3) states that ''When a coloring has been added to butter, cheese, or ice cream, it need not be declared in the ingredient list unless such declaration is required by a regulation in part 73 or part 74 of this chapter to ensure safe conditions of use for the color additive.''

Because of literature reports of allergic-type reactions to FD&C Yellow No. 6, the agency is now proposing to require the declaration of FD&C Yellow No. 6 on labels for butter, cheese, and ice cream. Because of these reports, the agency is also proposing to require the declaration of FD&C Yellow No. 6 as an ingredient when it is used in drug products that are administered to mucous membranes.

II. Possible Allergic Reactions to FD&C Yellow No. 6

A. Review of Literature

FD&C Yellow No. 6, an azo dye, is defined in § 74.706(a)(1) and (b) (21 CFR 74.706(a)(1) and (b)). Uncertified FD&C Yellow No. 6 is commonly known as sunset yellow or sunset yellow FCF. Several published articles report allergic-type reactions to FD&C Yellow No. 6 (Refs. 1 through 12). One of these, a case study reported by Jenkins et al. (Ref. 1), was cited as evidence of the allergenic nature of FD&C Yellow No. 6 in a December 14, 1984, citizen petition concerning provisionally listed color additives. The agency, in denying that petition, noted that ''[T]he cited article is an isolated medical case report of an immunosuppressed, severely ill patient who was observed to experience gastrointestinal symptoms from sunset yellow powder (presumably uncertified FD&C Yellow No. 6) taken by mouth.'' The agency stated that it ''did not consider this single case report to provide a basis for concluding that FD&C Yellow No. 6 is an allergen.'' This information, however, together with the structural similarity of FD&C Yellow No. 6 to FD&C Yellow No. 5, which has also been reported to cause allergic-type reactions, prompted the agency to review all available information on allergic-type reactions related to the consumption of FD&C Yellow No. 6.

An early study reported evidence from dermal testing of sensitivity to FD&C Yellow No. 6 in a patient, but no response was elicited from administration of the color additive in a double-blind oral challenge test (Ref. 2). Subsequent studies suggested that patients could develop urticaria from consumption of azo dyes such as sunset yellow (Refs. 3 and 4). In another study, seven patients with allergic vascular purpura developed purpura after oral challenge with various azo dyes. One patient specifically reacted to sunset yellow (Ref. 5). Also, a case was reported of anaphylactic shock from exposure to FD&C Yellow No. 5 and FD&C Yellow No. 6 in soap used for a cleansing enema. The patient was reported to be sensitive to both color additives upon subsequent testing (Ref. 6). However, a double-blind clinical study of 43 asthmatic patients gave negative results for sunset yellow (Ref. 7).

The studies discussed above were questioned by interested parties in objections to the November 19, 1986, final rule with respect to their reliability as evidence that would justify label declaration of FD&C Yellow No. 6. The objections focused on the age of the studies and the procedures used by the clinicians. However, a more recent literature search has revealed other studies that were not discussed in the 1986 final rule.

In 1982, Ibero et al. (Ref. 8) published a study performed on 25 children with food allergy histories. To determine a cause for their symptoms, they were put through exhaustive tests, including: Case histories; cutaneous tests; determination of peripheral eosinophilia; determination of plasma immunoglobulins A, M, and G; determination of secretory immunoglobulin A in saliva; determination of total and specific immunoglobulin E against various food antigens; and being fed diets from which suspected food products were excluded. When these tests gave negative results, the patients were subjected to oral provocation with different food additives, including tartrazine and sunset yellow FCF after 48 hours of exclusion from their diets of dyes, benzoates, and salicylates. A lactose placebo was used in the study, but it is not clear whether the study was double-blinded.

Eight out of the 25 children challenged with sunset yellow reacted positively. Five of these had immediate positive reactions, and three had ''semi-retarded'' or ''retarded positive'' reactions (terminology used in the report). The agency is not considering the reported ''semi-retarded'' or ''retarded positive'' reactions as positive to sunset yellow because it is unclear what is meant by this terminology. Although 5 positive reactions out of 25 patients is a large percentage, the agency