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CONSUMER HEALTHCARE PRODUCTS ASSOCIATION®

May 4, 2001

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Rockville, MD 20857

RE: Docket No. 98P-0610

SUBJECT: Comments on FDA's Background Materials Relating to May 11, 2001 Joint Meeting of the Nonprescription Drugs Advisory Committee and Pulmonary Allergy Drugs Advisory Committee

To Whom It May Concern:

The Consumer Healthcare Products Association (CHPA) submits these comments in response to the Citizen Petition by Blue Cross of California (WellPoint Health Network) on the subject of switching three second-generation antihistamines: cetirizine, fexofenadine, and loratidine.

CHPA is the 120-year old trade organization representing the manufacturers and distributors of nonprescription medicines and dietary supplements. CHPA has over 200 members across the manufacturing, distribution, supply, research, and advertising sectors of the self-care market. By sales, CHPA members marketing over-the-counter (OTC, nonprescription) medicines represent over 90% of the U.S. OTC marketplace. Over the years, CHPA has commented to the agency on virtually all aspects of OTCness, and specifically on Rx-to-OTC switch. Both the conceptual and procedural aspects of Rx-to-OTC switch are areas of high interest and priority for CHPA members.

CHPA's comments fall into two areas: approval of drugs on their own merits and sponsorship of switch applications.

I. Drugs Are Approved on Their Own Merits, Not on a Comparative Basis

Rx-to-OTC switches and other OTC new drug approvals have consistently been undertaken on a case-by-case basis through a data-driven process that brings the best current science to bear on the public health decision of widespread OTC availability. The

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OTC drug approval process, and specifically the Rx-to-OTC switch process, has been highly successful, with more than 80 ingredients, dosages and dosage forms switched since the start of the OTC Review in 1972.

Importantly, nowhere in the statute or in the regulations is there a stipulation that OTC drug approvals should be undertaken on a comparative basis, either in relation to other drugs currently on the OTC market or those that might be switched to the OTC market. The Food, Drug Cosmetic Act was carefully written to provide that drugs should be made available to consumers if FDA concludes that they are safe, effective, and properly labeled. Once approved, a product can be withdrawn only on a finding that it is no longer safe or effective. The availability of a "better" drug is not a criterion for withdrawal.

The effectiveness standard in the FD&C Act is not a comparative standard. This is borne out in the legislative history of the 1962 drug amendments. Testifying in favor of the bill that would become the 1962 drug amendments, the Secretary of Health, Education, and Welfare explained that "the bill furnishes no basis for ... apprehensions" that the agency would be able to make approval decisions based on "comparative efficacy of a new drug in terms of drugs already on the market." [1] The subject of comparative efficacy (also termed "relative efficacy") was further queried by Senator Carroll and received this reply from Secretary Ribicoff: "We do not seek the authority [to determine relative efficacy of drugs]...we would not and do not intend and do not want to pass on relative efficacy. This is no power we seek and no power we desire" [2] FDA Commissioner Larrick made the same point: that determination of effectiveness would not involve consideration of the relative efficacy of one drug compared with another.[3]

In isolated instances involving very serious adverse events, the safety of a drug can be a comparative issue. Such instances are rare, most likely in relation to mortality or severe morbidity, and would be even less likely to arise in the OTC context than with prescription drugs, because OTC drugs by definition have a wide margin of safety and a safety profile that has been well-characterized before approval of the product for nonprescription use.

Thus, the decision to approve a drug for widespread OTC use is solely a decision based on whether labeling can be written for the safe and effective use of the specific product (or ingredient) by consumers without a prescription; it is not to be based on decisions about a drug's comparative safety or effectiveness profile.

It is important to note the following. The first generation OTC antihistamines have a number of generally-recognized safe and effective uses including those relating to: upper respiratory symptoms associated with hayfever and allergic rhinitis; runny nose

[1] "Drug Industry Antitrust Act." *Hearings before the Subcommittee on Antitrust and Monopoly of the Committee on the Ju.diciary. U.S. Senate*, 87th Cong. 1st Sess. 2585 (1961) (statement of Abraham Ribicoff)
[2] *Id.* At 2605
[3] *Id.* At 2606; see also S. Rep. No. 1744, 87th Cong., 2nd Sess. 16 (1962).

and sneezing due to colds and flu; and topical use for itching associated with insect bites, minor skin irritations and rashes due to poison ivy, poison oak and poison sumac. The pharmacological basis of these intended use of first-generation OTC antihistamines as well as their individual side effect profiles are generally well known and predictable.

In the background materials for the May 11th advisory committee meeting, FDA is very explicit that its safety review of the first-generation OTC antihistamines is not intended to be "comprehensive" nor "to suggest that there may be safety issues pertinent to the continued marketing of these products in this country".[4] Indeed, FDA concludes in the materials that these first-generation antihistamines are "generally-accepted as appropriate OTC drugs."

The labeling of OTC antihistamines for these uses has been developed through an extensive public review and comment procedure under the OTC Review and thereby defined in the relevant OTC monographs for allergy and cough/cold products.

II. It Would Be Poor Public Policy for FDA to Initiate Switches Without the Support of the Sponsor.

The NDA holder – the company that developed the drug for prescription use -- knows the most about the drug and is in the best position to determine whether it would be appropriate to request a switch. Of course, FDA can and should consult with the NDA holder about whether the switch process should be initiated, but switches pursued over the NDA holder's objection run the risk of prematurely or inappropriately removing prescription safeguards, to the detriment of the public health. In the only case in which FDA did switch a drug without the prior support of the sponsor (metaproterenol), extensive adverse comment ensued, and the agency moved quickly to rescind its decision. See 48 *Fed. Reg.* 24925 (June 3, 1983).

The agency lacks the legal authority to initiate a switch over the objection of the holder of the approved new drug application (NDA) for prescription use of the drug, at least without providing a formal evidentiary hearing.

Modern switches require extensive supporting data to demonstrate that the drug can be used safely and effectively, with proper labeling, on a nonprescription basis. These data can include reports of clinical studies, actual use studies, label comprehension studies, and epidemiological studies. With rare exceptions, the only way that these data will be developed is by the NDA sponsor through the submission of an NDA or NDA supplement. If FDA switched a drug over the sponsor's objection by relying on data in the sponsor's NDA without following the procedures set forth in the Hatch-Waxman Amendments, this would violate the sponsor's proprietary rights to its data. Since virtually any switch would have to be based at least in part on data in the prescription NDA, this is an additional legal restriction on the agency's ability to switch a drug

[4] See Background Materials for the May 11th Advisory Committee meeting at page 15.

without the sponsor's consent.

The switch regulation procedure set forth in section 503(b)(3) of the Act is ill-suited to the development and review of such data and, in any event, is an anachronism that has not been used since 1971. Switch petitions by third parties, unsupported by data comparable to what FDA requires in a switch NDA, must be summarily rejected. Moreover, the switch regulation process was never used by FDA to switch a drug over the objection of the sponsor. It would be inconsistent with FDA's historic practice to revive this mechanism and use it in a manner that is totally at odds with its use during the entire time in which the agency actively relied on it. Moreover, the switch regulation is only designed to remove the Rx legend. It is not designed to provide for the development of the significant data FDA demands to support the conclusion that consumers can use the drug safely and effectively without a doctor's intervention.

Regardless of whether FDA wished to resuscitate the switch regulation process, the agency could not switch a drug over the objection of the NDA holder without providing a formal evidentiary hearing. A switch would alter the fundamental conditions of approval by removing the Rx legend from a drug's labeling. FDA cannot do this over the sponsor's objection without following the hearing process established in section 505(e) of the Act and proving that the inclusion of the legend renders the drug's labeling false or misleading in accordance with that statutory provision and the agency's regulations (21 C.F.R. §§ 314.150, 314.200).

Congress did not intend the switch regulation process established in section 503(b)(3) to override a sponsor's hearing rights under section 505(e). Section 503(b)(3) was enacted as part of the Durham-Humphrey Amendment in 1951. This amendment enabled FDA to bring order to situations in which different companies marketed the same drug on Rx and OTC bases, by establishing that a particular drug (in the same dosage form and strength, and labeled for the same indication) must be marketed either as a prescription or nonprescription drug, but not both. There is no suggestion that Congress intended FDA to apply the provision in a way that overrides the hearing rights of an NDA sponsor when only one company currently is marketing the drug. Moreover, Congress amended the NDA provisions, including section 505(e), in 1962, more than ten years after passage of the Durham-Humphrey Amendment. Since it was modified later, section 505(e) should control over section 503(b)(3).

In any event, section 503(b)(3) does not specify what procedure is to be followed in issuing a switch regulation. While FDA reasonably may use informal rulemaking when a sponsor does not object, or when a large class of NDAs would be affected, fundamental principles of administrative law and due process require that FDA use a formal hearing process for switch rules issued under this section that affect a single or small number of NDA holders, regardless of the applicability of section 505(e), because the switch regulation constitutes an individual adjudication requiring a formal hearing. See, e.g., *Air North America* v. *DOT*, 937 F.2d 1427 (9th Cir. 1991) (agency must comply with both the Administrative Procedure Act and its organic statute); *Committee for Effective Cellular Rates* v. *FCC*, 53 F.3d 1309, 1318 (D.C. Cir. 1995) (an agency

"cannot, merely by invoking its rulemaking authority, avoid the adjudicatory procedures required for granting and modifying individual licenses"); *Civil Aeronautics Bd.* v. *Delta Airlines*, 367 U.S. 316 (1961) (regulation forcing modification of a single license required a hearing); *American Airlines, Inc.* v. *CAB*, 359 F.2d 624, 631 (D.C. Cir. 1966) (agency cannot undertake an "individual action . . . masquerading as a general rule").

Thus, the case law establishes "a recognized distinction . . . between proceedings for the purpose of promulgating policy-type rules or standards, on the one hand, and proceedings designed to adjudicate disputed facts in particular cases on the other" *United States* v. *Florida East Coast Ry. Co.*, 410 U.S. 224, 245 (1973). The switch of one or a small number of drugs falls clearly into the latter category rather than the former and therefore requires a hearing to resolve any dispute with the NDA holder. A hearing similarly is required under principles of procedural due process, because of the NDA holder's property rights in its approved NDA. See generally, e.g., *Barry* v. *Barchi*, 443 U.S. 55 (1979); *Ingraham* v. *Wright*, 430 U.S. 651 (1977).

FDA thus would face virtually insurmountable procedural obstacles to initiating switches over the objection of drug sponsors. If it pursued this path, it would find itself tied up in lengthy and burdensome hearings, quite possibly for years. It makes far more sense – not just legally, but practically as well – for FDA to continue to undertake its switch activities with the cooperation of sponsors. This way, drugs will be switched more quickly (where appropriate), more safely, and with more supporting data, all to the benefit of the public health.

For additional information or clarification of points made in this submission, please contact either of us at CHPA, telephone number 202-429-9260.

Sincerely yours,

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