



Consumer Healthcare
Products Association

October 31, 2005

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, room 1061
Rockville, MD 20852

Re: Docket No. 2005N-0345
FDA Request for Comments on Advance Notice of Proposed Rulemaking, "Drug Approvals: Circumstances Under Which an Active Ingredient May Be Simultaneously Marketed in Both a Prescription Drug Product and an Over-the-Counter Drug Product," 70 *Fed. Reg.* 52050-51 (September 1, 2005)

Dear Sir or Madam:

In the September 1, 2005, *Federal Register*, the Food and Drug Administration invited comments on the above-referenced advance notice of proposed rulemaking (ANPR), regarding circumstances under which an active ingredient may be simultaneously marketed in both prescription and nonprescription, or over-the-counter (OTC), drug products.

The Consumer Healthcare Products Association (CHPA), founded in 1881, is the national trade association representing manufacturers and distributors of OTC medicines and dietary supplements in the United States. CHPA members account for over 90 percent of the domestic retail sales of OTC medicines. As such, we have an interest in the subject matter of the ANPR. CHPA sees no need for the agency to initiate a rulemaking on this matter. Sufficient precedent already exists for an active drug ingredient to be simultaneously marketed in both prescription and OTC drug products based on narrow distinctions.

The comments below use the numbering and lettering for questions on which FDA has invited comments (see 70 *Fed. Reg.* 52051 [September 1, 2005]).

1. A. FDA does not need to initiate a rulemaking to codify its interpretation regarding when an active ingredient can be simultaneously marketed in both a prescription and OTC drug product, since ample precedents already exist to guide the agency and the public. As the agency notes in the background information of this ANPR, the 1951 Durham-Humphrey Amendments to the Food, Drug and Cosmetic Act removed the confusion that had existed prior to that time when different manufacturers made different decisions about whether to market a drug as prescription or OTC. Under the Durham-Humphrey Amendments, the same drug, at the same dosage form and strength,

and for the same indication, cannot simultaneously be available on a prescription and nonprescription basis.

But since the Durham-Humphrey Amendments, FDA has needed to draw fine distinctions among dosage forms, methods of administration, or indications or uses to regulate an ingredient differently in different settings. These fine distinctions are not limited to whether and when a drug ingredient is prescription or OTC. They run across a gamut of issues, from a product's primary mode of action to whether something is a food, drug, biologic, device, cosmetic, or some combination of them, from whether something is generally recognized as safe and effective or whether it requires a new drug application to other fine distinctions. The commonality in drawing these distinctions, and the very reason for drawing them, balances on whether or not an ingredient is the *same thing* in two related settings.

While FDA has established rules to help guide both interested parties and the agency in walking the line between various distinctions on what is or isn't the same and what triggers different treatment, there is no mandate to do so in every instance. In the case of the instant question of prescription and OTC status, there is no need for a rule, as there are ample precedents to give interested parties paths to follow to distinguish among different labeling requirements, leading to a drug active ingredient in two or more settings not being the "same," even if an outside observer less familiar with the nuances involved would not immediately see the distinctions. There are any number of instances where an active ingredient is seen as an OTC drug in one dosage form and strength for a specified indication(s), and also has uses or additional labeling under consultation with a health professional, whether those different uses or labeling are termed prescription use, professional labeling, professional information, or even off-label use.

The examples which follow provide a partial, not exhaustive, list of those instances where a particular ingredient is seen as an OTC drug in one or more settings, but is a prescription drug or includes prescription labeling, professional labeling, or professional information in others.

(1) Dosage strength variations. As FDA notes in the ANPR, ibuprofen and H2 blockers are both examples in which an ingredient is prescription in one strength and OTC in another. While FDA also pointed to more readily distinguished differing strengths and indications for the prescription or OTC ibuprofen and H2 blocker examples in the ANPR, one can also point to dosage strength variations where the distinctions between the prescription and OTC versions are finer. For example, prescription-strength 2.5 percent hydrocortisone cream is indicated for relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. OTC 1.0 or 0.5 percent hydrocortisone cream is indicated for temporary relief of itching associated with minor skin irritations, inflammation, and rashes due to a number of listed inflammatory and pruritic conditions; i.e., indications closely related to the higher-dose prescription indication.

As another example, the directions for OTC ibuprofen start at 200 mg, and go up to 400 mg per dose, for aches, pains (including the pain of menstrual cramps), minor pain of arthritis, and reduction of fever. While higher strengths of prescription ibuprofen are available, prescription strength formulations start at 300 mg, between the two OTC doses. In addition, arthritis, including flare-ups of chronic disease, mild to moderate pain, and primary dysmenorrhea are prescription indications. These indications are closely related to the OTC indications.

(2) Indication variations. In addition to dosage strength variations (some of which include very similar indications, including the examples mentioned earlier), there are prescription and OTC variations based on the indication using the same dosage strength. Ibuprofen again provides an example, where children's ibuprofen is available OTC for children down to 6 months of age in a suspension -- 100 mg/5 mL -- to temporarily reduce fever or to relieve minor aches and pains due to listed common conditions. The same strength is available as a prescription for children down to 6 months of age for reduction of fever, for relief of mild to moderate pain, and for relief of signs and symptoms of juvenile arthritis. Setting aside the juvenile arthritis indication, which can be readily distinguished, the OTC "'temporarily' reduce fever" indication versus the open-ended prescription "reduction of fever," and the OTC minor aches and pains versus the prescription mild to moderate pain indications illustrate the fine line between two products distinguished as not being the "same."

Clotrimazole is a second example, where 1 percent topicals are available: • OTC for athlete's foot, jock itch, or ringworm; • OTC for treatment of recurrence of symptoms matching a previously diagnosed vaginal yeast infection; and • prescription for treatment of candidiasis due to *Candida albicans* and tinea versicolor due to *Malassezia furfur*. (There are differing creams, lotions, solutions, or delivery vehicle variations in this example. There are also additional strengths for different treatment durations for vaginal yeast infections.) Again, OTC labeling for recurring vaginal yeast infections versus the prescription labeling for open-ended occurrence/recurrence and with reference to more specific causes of the condition draws a fine line between related contexts that aren't seen as the same. It is worth noting that the first reference to the fact that the OTC product is for recurring infections does not occur in the "use" section of the OTC outer package label. Rather, the direction to consult a doctor if this is the first vaginal itch situation occurs under "warnings" – a different section of the OTC "Drug Facts" label from the "use" section.

(3) Professional labeling approaches. Under the OTC Review monograph system, many ingredients or classes of ingredients that are generally recognized as safe and effective (GRAS/GRAE) include professional labeling. While it is true that the OTC products with these ingredients are not technically prescription products at the same time, the limitation that this professional labeling is to be provided to health professionals but not to the general public serves the same practical intent: it distinguishes between OTC information (i.e., those uses that are safe and effective for consumers, or information intended to provide for safe and effective use by consumers on the basis of labeling), and information or uses that are intended to be limited to use under the professional

supervision of a health practitioner because of potentiality for harmful effect; method of use; or collateral measures necessary to use (i.e., factors in the definition of a prescription drug under 503(b)(1)). Among the many monographs or tentative final monographs with professional labeling are:

- **Antacids:** Professional labeling for antacids includes additional details on the neutralizing capacity of the product in terms of dosage per minimum time interval; additional indications (for specific disease states or, for certain ingredients, low phosphate diets); additional warning information on kidney disease for certain ingredients where the OTC label includes a contraindication for kidney disease; and additional warning information on prolonged use for certain ingredients where the OTC label includes a duration of use warning. See 21 CFR sec. 331.80 (April 2004) on professional labeling, and 21 CFR sec. 331.30 (April 2004) on OTC labeling of antacid products.

- **Antiflatulent:** Professional labeling here distinguishes between the basic OTC indication to relieve gas symptoms and indications tied to a particular subpopulation's state: gas pain in postoperative or endoscopic exam settings. See 21 CFR sec. 332.31 (April 2004) on professional labeling compared and contrasted to OTC labeling at 21 CFR 332.30.

- **Topical antifungals:** Professional labeling for a specific antifungal ingredient includes an additional indication for superficial skin infections caused by yeast (*Candida albicans*). See 21 CFR 333.280 (April 2004) on professional labeling compared and contrasted with the OTC indications for athlete's foot, jock itch, and ringworm at 21 CFR 333.250.

- **Cough, cold, allergy, bronchodilator, and antiasthmatic OTCs:** Here again professional labeling includes additional information that may be provided to health professionals, but not to the general public, in this instance focused on age distinctions, including dosage schedules for children 6 years of age to 12, and children 2 to under 6. See 21 CFR 341.90 (April 2004). Similar to the case of antiflatulents, professional labeling in the category includes a narrow distinction within the indication for an expectorant tying the expectorant to an underlying condition, but without changing the basic indication: “*helps loosen phlegm (mucus) and thin bronchial secretions to*” (select one or more of the following: ‘rid the bronchial passageways of bothersome mucus,’ ‘drain bronchial tubes,’ and ‘make coughs more productive’)” for the OTC indication compared or contrasted with professional labeling that the expectorant “*helps loosen phlegm and thin bronchial secretions in patients with stable chronic bronchitis.*” (Emphasis added.) Compare and contrast 21 CFR 341.78 (April 2004) for OTC expectorant labeling with 21 CFR 341.90(d) for professional labeling.

- **Miscellaneous internal OTC products:** Cholecystokinetic drug products are GRAS/E for OTC use, and again a distinction is made between

consumer labeling and labeling provided to health professionals but not to the general public. Here, the consumer's OTC indication is for the contraction of the gallbladder during diagnostic gallbladder studies, and consumers are directed to take the product only when instructed by a doctor. Left to professional labeling is a description of the implicit 'how' (visualization) of the OTC indication's explicit 'what' (for diagnostic studies): "For visualization of biliary ducts during cholecystography." See 21 CFR 352.350 on OTC labeling and 352.280 on professional labeling. In this final example, there is no free-standing separate indication, or no separate dosage form or strength, to distinguish between the OTC use and the professional (i.e., prescription-like) use. Indeed, in this example, OTC use would be predicated on the ultimate professional use. The example yet again illustrates the fine lines that can be drawn.

With OTCs subject to a new drug application, FDA has also worked with companies on professional labeling or professional information within the approved labeling. For example, at least one of the H2s includes not only strength or indication differences between prescription and OTC versions of the ingredient, but professional information for the OTC version discussing pharmacokinetic interactions. Overdosage information provided as professional information in labeling for a number of OTC internal analgesics or antidiarrheals are further illustrations.

(4) Age distinctions. As covered in the discussion above on professional labeling, age is frequently used to distinguish either OTC labeling from prescription labeling for the same active ingredient, OTC labeling from professional labeling or professional information, or OTC labeling from an off-label use a physician could choose to prescribe for a patient.

In addition to the GRAS/E OTC ingredients discussed earlier, another example would be nicotine replace therapy, where the directions advise potential users to ask a doctor before use if under 18 years of age. NRT products are further labeled as not for sale to those under 18 years or age, and labeling states that proof of age is required. While a version of these products is not labeled for prescription use for those under 18, a doctor, upon being asked, could chose to prescribe an NRT product within their own practice of medicine.

The same can be said for minoxidil in either 5 percent strength for men, or 2 percent strength for women, where the labels warn against use if you are less than 18 years old.

Clotrimazole for recurring vaginal yeast infections or H2s for heartburn are further examples along the lines of NRT and minoxidil, this time with labeling for use in those 12 and over. (Clotrimazole for athlete's foot, jock itch, and ringworm, meanwhile, warns against use on children under 2.)

In the case of H2s, similar to NRT, the OTC directions are to ask a doctor for children under 12. How a doctor might respond is not addressed, instead being left to

their discretion within the practice of medicine. (Meanwhile, prescription versions of the H2s exist in a variety of other strengths.)

Age distinctions for children who are 6 years of age versus those under 6 are even more common. In addition to the GRAS/E illustrations given earlier, the antidiarrheal loperamide, with OTC directions to ask a doctor before use in children under 6 years of age, includes a professional dosage schedule for children 2-5 years old.

(5) Gender distinctions. Distinctions have also been drawn between ingredients in OTC products versus other, prescription, professional information, or presumably off-label uses based on gender. Clotrimazole, discussed earlier, would be one example. Minoxidil would be another.

Minoxidil 5 percent topical solution to help regrow hair is indicated for use in men, and includes warnings against use by women (at the same time, it is not exempt from a general OTC warning to seek the advice of a healthcare professional if the user is pregnant or nursing a baby). Minoxidil 2 percent, meanwhile, is marketed under a brand including a descriptor within the brand name of “For Women.” The labeling, however, includes no uses, warnings, or directions limiting its use to women. Earlier versions of OTC minoxidil 2 percent included separate packages and separate labeling for a brand including “for Men” within its brand name, and a version including “for Women” within its brand name. With earlier versions, warnings were included on the “for Women” brand specific to women that were not included in the “for Men” brand (such as the pregnancy/nursing warning). Compare and contrast the “for Men” and “for Women” versions as published in Physicians’ Desk Reference for Nonprescription Drugs (1997 edition, Medical Economics). While there neither were nor are simultaneous prescription and OTC versions of an ingredient in the minoxidil example, it nonetheless again points to the ability of manufacturers and FDA to draw fine distinctions between two items to make them not the same.

B. and C. Given the precedents that already exist, there should not be significant confusion regarding section 503(b), so the question of dispelling confusion is moot. As discussed above, distinctions -- some broad, some narrow -- have been used for a range of ingredients to allow the ingredient to be labeled and marketed in more than one way, so there should not be significant confusion regarding section 503(b). A range of paths and precedents exist for both the agency and those wishing to label and market a drug product. The question of dispelling confusion is moot.

2. A. and B. Existing law is clear as to what parties the Food, Drug and Cosmetic Act applies, and existing practice and precedent already recognizes this, already answering the question of whether or how FDA can limit OTC sale of a product to a particular subpopulation. FDA’s question as to the practicality of enforcing a limitation on prescription versus OTC status misses the mark. Whether one likes to admit it or not, the Food, Drug and Cosmetic Act does not and cannot apply to every setting in which any FDA-regulated product is ultimately used. FDA does not regulate the practice of medicine. Apart from limited exceptions, FDA does not control the practice of

pharmacy. FDA cannot control the behavior of individual citizens, and that is true whether an active ingredient is OTC, prescription, or both.¹ FDA does, of course, have an obligation to protect and advance the public health by assuring that drugs are safe, effective, and appropriately labeled. Similarly, our members, as manufacturers of OTC medicines, not only have to meet FDA requirements, but also work to encourage consumers to use their products responsibly in accordance with labeling, and have a need to determine the intended use of their products.

While one can speculate as to what has changed in 2005 to raise the question of FDA's ability to enforce a labeling limitation to a particular subpopulation, the fact remains that this issue has always been present. The issue is present when a child is 5 years and 363 days old versus 6, not quite 12 versus 12, or not quite 18 versus 18. It is present when a potential user is a man or a woman. It is present when a condition is occurring temporarily or for the first time versus when it is for a chronic condition or recurring. Yet this is not to say manufacturers or FDA is without means to test, encourage, and improve concordance with label directions. Over generations, the tests and measures by which a manufacturer's and FDA's best intentions for how a product can and should be used have grown. For the current generation of prescription-to-OTC switches, label comprehension studies and actual use studies have become the norm, or at least the norm for early entrants into a new category. Label comprehension studies seek to assure that a proposed OTC label adequately communicates -- i.e. that people understand it -- by testing label versions through an iterative process, with variations in wording, emphasis, or positioning of information. Actual use studies try to simulate the OTC purchase environment by limiting healthcare provider involvement and removing the trial from the clinical setting. The focus of actual use studies is on self-selection (i.e., do the appropriate people chose to use the product and do the inappropriate people de-select, or chose not to use the product), compliance with package labeling, and safety in a minimally supervised environment. Label comprehension, self-selection, or actual use studies have been publicly considered and discussed at FDA advisory committee meetings concerning proposed prescription-to-OTC switches (be they successfully switched, rejected, or pending) for ingredients such as minoxidil, cholesterol-lowering therapies, an analgesic for a migraine indication, a muscle relaxant, a contraceptive sponge, omeprazole, and levonorgestrel, among others.

FDA officials (noting the opinions expressed are those of the speaker, and do not necessarily represent those of the Food and Drug Administration) have discussed the usefulness (including value and limitations) of label comprehension or actual use studies at a range of meetings, including Drug Information Association meetings, CHPA Regulatory and Scientific Conferences, and others.

¹ As just one example on the non-use of medicines, two out of five senior citizens said they hadn't taken all the medicines their doctors prescribed for them over the year before being surveyed – either because they didn't think the drugs were helping them, they didn't think they needed them, or they were concerned about costs. See Safran, et al., "National Survey of Seniors and Prescription Drugs, 2003," available in Health Affairs online edition, April 2005, <http://content.healthaffairs.org/cgi/reprint/hlthaff.w5.152v1?ijkey=Gn1EKoVVrGMv.&keytype=ref&siteid=healthaff>.

The point is that manufacturers and FDA are working toward improved understanding and predictability in how consumers understand and intend to use OTC medicines. We are better equipped today than in the past to assess how well new products will measure up against that goal.

3. A. It is not clear whether or not different **marketed** and specifically distributed Rx and OTC products may be sold in the same package, but it **is** clear that prescription uses for a specific OTC product can be accomplished with one package. The agency asks whether, assuming it is legal to market the same active ingredient in both a prescription and OTC product, different products may be legally sold in the same package. Given the fine distinctions to what is or isn't the "same," the answer would appear to be highly case specific, based on how and for what purpose a given product was being marketed. In some of the examples provided earlier, the manufacturer and FDA evidently reached a judgment that different packages were appropriate to distinguish otherwise more closely similar products from one another. Clotrimazole and some of the H2s are examples of this. While both of the original minoxidil 2 percent versions were OTC, they were in different packages. In contrast, in the professional information examples, including explicit dosage instructions based on the age of a child, different packages were not the end result.

B. While not entirely clear as a broad rule, there are circumstances where it would be inappropriate to sell two marketed products, one Rx and one OTC, in a single package. Finally, FDA asks, if two products may be lawfully sold in a single package, under what circumstances would it be inappropriate to do so? As with the previous question, given the fine distinctions that are sometimes drawn, the answer would appear to be highly case specific. Factors FDA and a manufacturer might consider in answering a case-specific question could include reducing consumer confusion, assuring data exclusivity protections are accounted for, or ease of use, among others. In both the simultaneous prescription and OTC realm, and the OTC realm, there are any number of examples where distinctions in indications, dosage forms, or strengths have led to separate packages, which in turn reduces the chances of consumer confusion, addresses data exclusivity rights, or eases use. Antifungals (dosage form distinctions, indication distinctions, and/or strength distinctions); an ingredient which can be either an antihistamine or a sleep aid (indication and strength distinctions); minoxidil (gender and strength distinctions); and analgesics (strength and/or indication distinctions) are examples with separate packages.

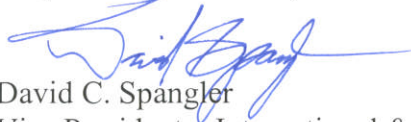
Conclusion.

While the *same* drug, at the same dosage form and strength, and for the same indication, cannot simultaneously be available on a prescription and nonprescription basis, FDA has long needed to draw fine distinctions among dosage forms, strengths, methods of administration, indications or uses, or on other bases to distinguish between OTC and prescription versions of the same active ingredient, or between OTC labels and professional information/labeling for the same active ingredient.

In other areas apart from this ANPR, FDA in some instances has established rules to help guide both interested parties and the agency in walking the line between various distinctions on what is or isn't the same and what triggers different treatment, but there is no mandate to do so. In the case of the instant question of prescription and OTC status, there are ample precedents to give interested parties paths to follow to distinguish among different labeling requirements, leading to an active ingredient in more than one setting not being the "same," even if an outside observer less familiar with the nuances involved would not immediately see the distinctions.

Given the existing precedents, we see no need for the agency to initiate a rulemaking to codify its interpretation regarding when an active ingredient can be simultaneously marketed in a prescription and OTC drug product.

Respectfully submitted,



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