Advancing Quality Healthcare
Through Over-the-Counter Medicines
and Nutritional Supplements

FOUNDED 1881

CONSUMER HEALTHCARE PRODUCTS ASSOCIATION

July 21, 2004

Division of Dockets Management
U.S. Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Docket No. 2003N-0342
RIN 0910-AC35
Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products, Proposed rule, 69 *Federal Register* 21778 (April 22, 2004)

Dear Sir or Madam:

In the April 22, 2004 *Federal Register*,[1] the U.S. Food and Drug Administration ("FDA") published and invited comments on the above-referenced proposed rule, which is intended to bring FDA regulations into compliance with section 17 of the Best Pharmaceuticals for Children Act ("the BPCA").[2]

As proposed, the rule would require the labeling of every human drug product for which an application is approved under section 505 (21 U.S.C. § 355) of the Federal Food, Drug, and Cosmetic Act ("the FDC Act") to include: (1) A 800 toll-free number maintained by FDA for the purpose of receiving voluntary reports of adverse events (or "side effects") regarding drugs, and (2) a statement that the number is to be used for reporting purposes only, not to seek or obtain medical advice.[3] FDA would allow affected entities one year following the effective date of any final rule published in the *Federal Register* to be in compliance.

---

1 "Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products," 69 *Fed. Reg.* 21778 (April 22, 2004). In a subsequent entry in the *Federal Register*, FDA corrected inadvertent errors related to the assigned Docket No. ("2003N-0324" changed to "2003N-0342"). *See* 69 *Fed. Reg.* 31773 (June 7, 2004).

2 Public Law No. 107-109.

3 We note, however, that the actual required labeling statement proposed for reporting purposes is: "You may report side effects to FDA at 1-800-FDA-1088." The exclusion of requests for medical advice, not to mention questions and/or concerns about non-safety-related matters, is not addressed.

The Consumer Healthcare Products Association ("CHPA"), founded in 1881, is the national trade association representing manufacturers and distributors of over-the-counter ("OTC") drugs and dietary supplements in the U.S. Currently, CHPA members account for over 90 percent of the retail sales of OTC drugs in the U.S. CHPA has been a major participant in every aspect of the OTC Review process since its inception in 1972.

A substantial portion of the CHPA membership is affected directly by the proposed rule. Although CHPA recognizes the importance of obtaining complete and accurate adverse event data for drug products and has actively supported the mandatory reporting of adverse events for OTC drugs, the proposed rule fails to fulfill the goals of the BPCA in several important respects. It fails because:

1. Congress intended the 800 toll-free number labeling requirement to apply to prescription drugs only, not to OTC drugs;

2. The proposed rule would do more harm than good because multiple 800 toll-free numbers on the OTC label would needlessly confuse certain consumers taking OTC drugs and could lead to injuries that might have been avoided;

3. The ambiguity of the term "side effects" makes extremely difficult the consumer or layman's task of distinguishing a legitimate side effect (as contemplated by FDA in the proposed rule) from one that is not and could put the consumer at risk while leaving the question of "actual causation" unresolved;

4. The proposed rule would result in a wholesale depletion of FDA's limited resources because MedWatch staff would receive thousands of reports wholly unrelated to safety;

5. The proposed rule would effectively undo the value of FDA's mandatory adverse event reporting program because adverse event data related to potential product quality or safety problems or critical information related to good manufacturing practices ("GMP") complaints could not be investigated as actively or timely by manufacturers as possible;

6. FDA's estimate of the number of stockkeeping units ("SKU") affected by the proposed rule has been grossly underestimated; and

7. FDA has also underestimated the potential new compliance costs to revise the product labeling of affected SKUs.

For these reasons, CHPA urges FDA to fulfill the intent of Congress and not apply the rule to OTC drugs.

1. Congress intended the 800 toll-free number labeling requirement to apply to prescription drugs only, not to OTC drugs

The proposed rule fails to fulfill the goals of the BPCA because Congress intended the 800 toll-free number labeling requirement to apply to prescription drugs only, not to OTC drugs. Under section 17 of the statutory amendment, the rule promulgated by the Secretary must "seek to minimize the cost of the rule *on the pharmacy profession*" (emphasis supplied). Similarly, the legislative history/intent of the BPCA emphasizes that "*pharmacists*…include the phone number *with all prescriptions*," "the best way to reach the 'broadest consumer audience' is to include the toll-free number *on the prescription bottle, vial, etc.,* perhaps in the form of auxiliary labels," and that "*pharmacists*, who are already overburdened, do not have their workload increased…" (CBO Cost Estimate; Committee on Energy & Commerce Analysis; emphasis supplied).

These multiple references to pharmacies and prescriptions without a corresponding mention of OTCs plainly indicate Congress' clear intent to limit the requirement to prescription drugs. The BPCA does not mention the cost to the OTC drug industry. Nor does the BPCA's legislative history/intent address the mandatory inclusion of the phone number with all OTCs, the mechanics of changing the OTC label, or the cost to implement the labeling change to the OTC drug industry.

That Congress never intended the 800 toll-free number labeling requirement to apply to OTC drugs is evidenced (in part) by FDA's inability to fashion a flexible method(s) of compliance for OTC drugs under the proposed rule. Pharmacists primarily dispense prescription drugs, and can efficiently affix stickers (or "auxiliary labels") to drug vials or revise Rx computer printouts or consumer medication information to include the MedWatch information in a relatively short time frame. The flexibility that pharmacists are permitted when it concerns labeling changes for prescription drugs is evident in the proposed rule itself.

FDA states that it "proposes to exercise discretion to give affected pharmacies flexibility to select a method of compliance from among five options that would minimize the impact of the proposed rule."[4] The Agency's motivation for providing five options as opposed to just one is "[t]o minimize the cost of the requirement for

[4] 69 *Fed. Reg.* at 21783.

pharmacists to distribute the side effects statement…"[5] The five options identified by FDA are:

> (1) Attach a standard-size sticker (1½ by 7/16 inches) containing the side effects statement to the vial, package, or container of the prescription drug product; (2) use a pharmacy prescription vial cap preprinted with the side effects statement; (3) distribute a separate sheet of paper containing the side effects statement; (4) distribute consumer medication information such as that provided by pharmacy software and third party data processing vendors that contains the side effects statement; or (5) distribute the appropriate FDA-approved Medication Guide that contains the side effects statement.[6]

In sharp contrast, FDA only identified one method of compliance for manufacturers of OTC drugs under the proposed rule. That is, FDA modified the side effects statement for OTC products to correspond to the drug facts format under 21 C.F.R. § 201.66.[7] In FDA's view, "[t]his approach incorporates the side effects statement in OTC product labeling in the appropriate location, using existing consumer-friendly language and a minimal amount of additional labeling space."[8]

Nonetheless, the imbalance between FDA's approach to OTC drugs and its approach to prescription drugs remains. FDA says nothing about exercising "discretion" or offering "flexibility" to affected OTC drug manufacturers. Moreover, unlike prescription drugs, it is not feasible to over-sticker OTC products or revise computer printouts or consumer medication information. The lack of available space on the product carton due to other required labeling information makes over-stickering infeasible as an option. And individualized computer printouts are not feasible for OTC drugs, which are pre-packaged. Accordingly, as a matter of compliance, the cost being assessed by FDA on the OTC drug industry, whether inadvertent or not, exceeds that of the prescription drug industry and amounts to a penalty.

---

5 69 *Fed. Reg.* at 21781.

6 69 *Fed. Reg.* at 21781.

7 *See* 69 *Fed. Reg.* at 21780-81 ("3. OTC Labeling").

8 69 *Fed. Reg.* at 21781.

To remedy these concerns, FDA should follow the lead of Congress on this issue, and revise the proposed rule by making application of the 800 toll-free number labeling requirement exclusive to prescription drugs only.

2. The proposed rule would do more harm than good because multiple 800 toll-free numbers on the OTC label would needlessly confuse certain consumers taking OTC drugs and could lead to injuries that might have been avoided

OTC drugs for oral administration must bear a general label warning that "In case of overdose, get medical help or contact a Poison Control Center right away." A similar warning is required for drugs not intended for ingestion that are swallowed.

We understand that legal counsel within the Center for Drug Evaluation and Research ("CDER") at FDA is developing a proposed rule to require the labels of these OTCs to include the Poison Control Center toll-free number. Thus, an OTC drug approved under a new drug application ("NDA") could eventually be required to bear two toll-free numbers for related purposes. Furthermore, as explained below, many companies already include their own 800 toll-free numbers on OTC labels, which afford consumers easy access to report any product-related issues or other problems. Thus, consumers could eventually have to decide among three different numbers to call to report a potential quality, adverse event, or some other issue.

Consumers could easily be confused by one 800 toll-free number to report side effects, another 800 toll-free number to contact a Poison Control Center, and a third 800 toll-free number provided by the company. In a poisoning emergency, for instance, a consumer might mistakenly contact MedWatch instead of the Poison Control Center. This could lead to injuries that might have been avoided if the Poison Control Center had been contacted promptly. Companies with their own 800 toll-free numbers maintain forwarding links to Poison Control Centers for emergencies. FDA has no such system. The cost to implement such a system at FDA would be prohibitive.

3. The ambiguity of the term "side effects" makes extremely difficult the consumer or layman's task of distinguishing a legitimate side effect (as contemplated by FDA in the proposed rule) from one that is not and could put the consumer at risk while leaving the question of "actual causation" unresolved

The proposed rule directs the labeling of OTC drug products approved under section 505 to state (in part) that –

"Stop use and ask a doctor if
■ side effects occur."

But the ambiguity of the term "side effects" makes extremely difficult the consumer or layman's task of distinguishing a legitimate side effect (as contemplated by FDA in the proposed rule) from one that is not. As a threshold matter, what constitutes a legitimate side effect? Is it only those side effects that are identified on the product label? Or is it a subjective determination that is patient-specific? To our knowledge, FDA has not conducted consumer label comprehension studies to determine consumer understanding of the words "side effects" and under what circumstances consumers would call the 800 toll-free number. For example, it is foreseeable that consumers could mistakenly call the 800 toll-free number for medical advice, even though FDA's proposal is for "reporting" purposes only.

An additional concern relates to consumer understanding. A perceived side effect may be unrelated to the use of the product or there may simply be no adverse event at all. As explained below, many companies already include their own 800 toll-free numbers on OTC labels, which afford consumers easy access to report any product-related issues or other problems. But reports of adverse events constitute only a minute fraction of the calls that these companies receive each year. Rather, the companies receive thousands of product inquiries or calls from consumers that are wholly unrelated to safety. They receive calls from consumers dissatisfied with things like a product's flavor, fragrance, or missing cents-off coupon, or who want their money back. Indeed, interpreting a non-safety-related matter as a side effect and then following the label's instructions by stopping use of the product in such unwarranted circumstances could needlessly prolong the consumer's underlying condition[9] and put him or her at risk of further complications.

The term "side effects" could also erroneously be construed to be conclusive with respect to a drug product. While a consumer may construe an adverse event to be related to a drug product that he or she has taken (e.g., stomach ache when taking aspirin), the adverse event may in fact be related to another condition or possibly another drug product he or she is taking. FDA regulations on reporting of adverse drug experiences establish that no conclusions about causality can be drawn from an adverse event report.[10] Moreover, the notion that OTC drug product warnings or similar regulatory action

---

[9] OTC drugs have been approved by FDA to treat a wide variety of ailments, such as preventing diseases like tooth decay, curing diseases like athlete's foot and, with a doctor's initial guidance, helping to manage recurring conditions like vaginal yeast infection, migraine and minor pain of arthritis.

[10] 21 C.F.R. § 314.80(k) ("*Disclaimer*. A report or information submitted by an applicant under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the applicant or FDA that the report or information constitutes an admission that the drug caused or

provides any evidence or allegation of "actual causation" has been repudiated expressly by FDA.

> Mandating warnings in an OTC drug product regulation does not require a finding that any or all of the OTC drug products covered by the regulation actually caused an adverse event, and FDA does not so find…Rather, as a consumer protection agency, FDA has determined that warnings are necessary to ensure that these OTC drug products continue to be safe and effective for their labeled indications under ordinary conditions of use…
> FDA's decision to act in this instance need not meet the standard of proof required to prevail in a private tort action (*Glastetter* v. *Novartis Pharmaceuticals Corp*., 252 F.3d 986, 991 (8th Cir. 2001)). To mandate warnings, FDA need not show, nor do we allege, actual causation.[11]

Nonetheless, the rule as proposed would have the practical effect of enticing plaintiffs' attorneys to file lawsuits against manufacturers of OTC drugs based on the data submitted to FDA under the 800 toll-free number reporting scheme. The resources necessary to defend against such frivolous allegations would be in the millions.

4. The proposed rule would result in a wholesale depletion of FDA's limited resources because MedWatch staff would receive thousands of reports wholly unrelated to safety

The Agency has requested industry comment on their experience with consumer telephone calls to toll-free numbers and the proportion of those calls related to safety issues.[12] Currently, many companies already include their own 800 toll-free numbers on OTC labels, which afford consumers easy access to report any product-related issues or other problems.[13] These companies have efficient systems for handling adverse events

---

contributed to an adverse effect. An applicant need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the drug caused or contributed to an adverse effect.").

[11] "Drug Labeling ; Orally Ingested Over-the-Counter Drug Products Containing Calcium, Magnesium, and Potassium," 69 *Fed. Reg.* 13725, 13729-13730 (March 24, 2004) (Final rule).

[12] *See* 69 *Fed. Reg.* at 21788.

[13] *See* 21 C.F.R. § 201.66(c)(9) (OTC drug product labeling telephone number requirement).

reported to them and, by law, report adverse events to the FDA for products approved under section 505 of the FDC Act.[14]

But reports of adverse events constitute only a minute fraction of the calls companies receive each year. Based upon data provided by CHPA member companies affected by the proposed rule, of approximately 1,154,700 calls received by companies, only 7% (or 83,500 calls) related to an actual adverse event. The reported incidence of "serious adverse events" was even less frequent, as it ranged from 0.2% to 0.6% of adverse event reports. One company further disclosed that approximately one-half (or 50%) of non-adverse event-related telephone calls ended up at or were ultimately routed to the 'adverse event only' phone line. There is no reason to believe that FDA's experience would be any different. In fact, it could be much worse.

FDA's MedWatch staff would receive thousands of product inquiries or calls from consumers that are wholly unrelated to safety. They would receive calls from consumers dissatisfied with things like a product's flavor, fragrance, or missing cents-off coupon, or who want their money back. The proposed rule's "side effects" language would encourage these reports.[15] The MedWatch staff is already heavily burdened, and does not have the resources to deal with spurious consumer complaints. The Agency would also incur increased costs (e.g., purchase of additional telephone and computer equipment, increased staffing) to handle the increased volume of calls.[16] FDA would be diverted from the principal MedWatch goal of receiving and monitoring adverse event information from physicians.[17]

5. The proposed rule would effectively undo the value of FDA's mandatory adverse event reporting program because adverse event data related to potential product quality or safety problems or critical information related to GMP complaints could not be investigated as actively or timely by manufacturers as possible

---

[14] *See* 21 C.F.R. §§ 314.80 and 314.98.

[15] Unlike the current MedWatch program, FDA is not proposing that consumers report only serious adverse events to the MedWatch program. As a result, this will result in more reports to FDA than under the existing system. *See* 69 *Fed. Reg.* at 21780.

[16] 69 *Fed. Reg.* at 21787 ("…if there is a substantial increase in the number of telephone calls, the agency might also incur fixed costs for additional telephone and computer equipment.").

[17] CHPA agrees with the Agency's suggestion that "[e]ven though health care practitioners are not the direct focus of the proposed rule,…the rule may cause an increase in direct reporting from health care practitioners" and that the "the impact on the agency could be substantial." 69 *Fed. Reg.* at 21787.

Reports that otherwise would be received by the company for mandatory reporting to FDA may be diverted to the FDA MedWatch number for voluntary reporting by consumers. The company may not be informed of critical information related to GMP complaints or potential safety problems with their products, and would have to file a Freedom of Information Act ("FOIA") request to obtain information about adverse events.

Currently, manufacturers monitor company 800 number calls about their marketed products to detect whether there may be a GMP or safety issue. Manufacturer monitoring of consumer calls leads to reporting of serious adverse events to FDA and allows a rapid response to product quality or safety issues. If the calls are diverted to the MedWatch number, where the only access manufacturers have to this information is through a lengthy FOIA process, the rule will impair companies' and FDA's ability to investigate and take quick action. There is also the potential for consumers to be exposed to product quality or safety problems longer than necessary. An otherwise avoidable delay in consumers receiving critical medical attention would follow.

Consumers also might file duplicate reports with FDA and the company, leading to duplicate adverse event reporting at FDA, which the agency and companies will need to sort through to eliminate. Based upon data provided by CHPA member companies affected by the proposed rule, company expenditures to address consumer confusion and the burden of sorting through duplicate reports could require hundreds of thousands of dollars per company per year. Duplicate reporting will produce a false positive signal for adverse events attributed to a particular drug. Furthermore, by scattering reporting across several receiving systems, the quality and statistical integrity of the data could easily be compromised, in addition to being difficult to coalesce, analyze, and interpret. FDA's commitment to "signal detection" would be hobbled.[18] This inability to interpret trends and forecast safety problems would place consumers in jeopardy.

6. FDA's estimate of the number of SKUs affected by the proposed rule has been grossly underestimated

FDA has requested comment on the number of SKUs affected by the proposed rule.[19] In FDA's estimate, there are "approximately 350 OTC products approved under an NDA and 172 approved under an ANDA."[20] Thus, the rule would "affect 522 OTC

---

[18] 69 *Fed. Reg.* at 21789 ("Reports of adverse drug events provide the agency with 'signals' that a drug product might have previously unidentified risks. Once a signal is detected, the agency can decide whether further action is necessary to protect the public health.").

[19] 69 *Fed. Reg.* at 21787.

[20] 69 *Fed. Reg.* at 21780.

products."[21] FDA further estimates that OTC products marketed under NDAs or ANDAs usually have 2 or 3 SKUs. Thus, based on its previous estimate, up to 1,050 branded packages and 520 private label packages might be affected by the final rule.[22]

But FDA's estimate regarding the number of SKUs per OTC product marketed under an NDA or ANDA and thus covered by the proposed rule has been grossly underestimated. Based upon data provided by CHPA member companies affected by the proposed rule, many OTC products approved under an NDA or ANDA have in the range of 6-12 SKUs per product. There are also some, however, with significantly more – up to 25, 50, even 70 SKUs in certain cases. The number of packages affected by the proposed rule will also be well in excess of the 1,570 figure put forth by the Agency (representing the sum of 1,050 and 520). Again, based upon data provided by CHPA member companies affected by the proposed rule, more than 2,700 SKUs will require revision. Accordingly, the reach and burden of the proposed rule will be significantly greater than FDA has forecast.

Once finalized, every affected OTC drug company will be competing for the same finite packaging and labeling resources for thousands of products approved under section 505. New cartons would have to be ordered from suppliers,[23] new artwork prepared, and new production lines set up. The time to re-label in this competitive atmosphere would be considerably greater than 13 months for many of the entities affected by the proposed rule.[24] The seasonality of certain products could cause a further increase (up to 2 years).

7. FDA has also underestimated the potential new compliance costs to revise the product labeling of affected SKUs

FDA has also requested comment on the potential new compliance costs to revise the product labeling of affected SKUs.[25] In FDA's estimation, revising labeling of branded OTC products may cost about $3,000 for each branded SKU and $1,000 for each

---

21 69 *Fed. Reg.* at 21787.

22 69 *Fed. Reg.* at 21787.

23 Many OTC cartons currently on the market are too small to be able to accommodate the 800 toll-free number language.

24 We note that compliance with, *inter alia*, the bar code label requirements could further contribute to this delay. *See* "Bar Code Label Requirements for Human Drug Products and Biological Products; Final Rule," 69 *Fed. Reg.* 9119 (February 26, 2004).

25 69 *Fed. Reg.* at 21787.

private label SKU.[26] Also, new compliance costs for OTC drug manufacturers may range from $1.2 million with one SKU per affected product to $3.7 million with three SKUs per affected product.[27]

Based upon data provided by CHPA member companies affected by the proposed rule, CHPA submits that revising labeling of OTC products will easily surpass FDA's projections of $1,000 or $3,000 per SKU. To comply with the proposed rule, the estimated total cost per SKU could run anywhere from $5,000 to $12,500, with many of those affected falling at or above the $5,000 mark. Personnel from resource groups including (but not limited to) planning, project management, quality, legal, regulatory, medical, marketing, and copying/printing would have to be tapped. The hours required to implement the necessary changes for a single SKU would be thirty-two (32), according to one member company. Total cost to comply with the proposed rule will top $5,000,000.

When this, the appropriate estimates of cost and number of SKUs per affected product are factored into the equation, it is clear that the new compliance costs for OTC drug manufacturers will be significantly greater than FDA has proposed.

Conclusion

In closing, for the reasons set forth, CHPA urges FDA to fulfill the intent of Congress by limiting the rule to prescription drugs only.

Respectfully submitted,

Paul J. Larsen, Esq.
Assistant General Counsel

cc: Daniel E. Troy, Esq. (GCF-1)
Steven K. Galson, M.D., M.P.H. (HFD-1)

[26] 69 *Fed. Reg.* at 21787.

[27] 69 *Fed. Reg.* at 21787.