Congress Readingy User Fee Program for OTC Products

Money Needed to Dig FDA Out of Its Review Ditch

Stephen Barlas

It was 11 years ago that pediatric health care practitioners raised concerns about the safety and efficacy of over-the-counter (OTC) cough and cold products in children younger than 6 years old. At hearings that year at the FDA, Joshua Sharfstein, MD, then Public Health Commissioner in Baltimore and eventually the FDA’s principal Deputy Commissioner during part of the Obama administration, stated: “Many reports and scientific papers document safety risks, including associations with 123 deaths between 1969 and 2006 among children from birth to 6 years of age. There are thousands of related poison control calls and emergency department visits each year. Unquestionably, these products fail to meet the statutory requirement of ‘generally recognized as safe and effective.’

A joint FDA advisory committee was nearly unanimous that same year in agreeing that new studies were necessary because extrapolation of efficacy data for the common cold indication from adults to children was not acceptable for children younger than 2 years old or for children 2 years to less than 12 years. The votes were 22 to 0 and 21 to 1, respectively, for the 2 age groups.

Today, however, the FDA has not taken any regulatory action against the makers of pediatric cough and cold products although the industry itself made some voluntary changes to labeling in 2008. That said, questions about the safety and efficacy of cough and cold products generally—components of one of the 52 FDA OTC monographs—and numerous other OTC products in other monographs are the driving force behind Congressional action to put a first-ever OTC user fee program in place. The OTC user fee bills, which have been approved by House and Senate committees, would give the agency a segregated fund of $22 million in the first year over and above what the FDA spends on OTC regulatory proceedings out of its normal Congressional appropriation. Those industry-supplied funds would supplement a niggling FDA budget for OTC product review that has lagged badly and has been unable to complete a review of approximately 125 active ingredients on the market that have not been designated as generally recognized as safe and effective (GRASE), the FDA’s standard for approval of new OTC drugs. David Spangler, Senior Vice President, Policy, and General Counsel, Consumer Healthcare Products Association, estimates those 125 active ingredients account for about 200 indications. There are also many products with GRASE active ingredients that have been waiting for years for the FDA to approve new warning labels or other changes.

An Overwhelmed, Understaffed FDA

Janet Woodcock, MD, Director of the FDA’s Center for Drug Evaluation and Research (CDER), told a House committee last year that the FDA is conducting 88 simultaneous rulemakings in 26 broad therapeutic categories encompassing hundreds of thousands of OTC drug products marketed in the United States. Many of those have been underway for years, some for decades.

It may be that uncertainties and frustration created by lagging FDA review of OTC products underlie some of the recent deal-making in the industry. Pfizer, Inc. has been trying to off-load its OTC business without any success. Procter & Gamble was a potential suitor, but decided instead to purchase the consumer health business from Germany’s Merck KGaA, which counts about $1 billion in annual sales from a portfolio of 10 core brands that are sold in more than 40 markets but not the United States. Glaxo had considered buying Pfizer’s unit but instead purchased Novartis AG’s 36.5% stake in their consumer-health joint venture for $13 billion.

In 2017, Bridgette L. Jones, MD, FAAP, testifying to Congress on behalf of the American Academy of Pediatrics, said, “The data that led FDA to label cough and cold medicines for children does not come close to meeting today’s standards for pediatric data. Not only that, but additional data gathered since that time has clearly shown certain cough and cold products to be completely ineffective in the pediatric population. Nevertheless, these products are still commonly marketed to children and often in combination with other products that can increase the safety risks.”

Spangler replied, “Pediatric cough and cold products were originally approved under different expectations and examined studies which do not meet today’s standards. As information comes to light over the years around safety, CHPA members have voluntarily made several packaging and labeling improvements to support the responsible use of these products and reduce accidental unsupervised ingestions. Furthermore, in May 2017, an article published in the medical journal Pediatrics concluded that OTC cough and cold medicines for children are safe when used according to the label and stored as directed.”

At the 2017 hearing, Scott Melville, President and CEO of the Consumer Healthcare Products Association (CHPA), underlined the utility of the monograph system, which he said has saved time and other resources for the FDA since there is no need to re-review each individual product with established ingredients that have already been proven safe and effective. For makers of these medicines, the system also saves time, resources, and provides for more efficient market. But he acknowledged, “Movement on unfinished items has ground to a halt, largely because the system is based on notice and

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Monograph Ins and Outs

The monograph system was established in 1972 and resulted in the establishment of 52 product categories, called monographs, such as Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (CCABADP). Each monograph lists approved products in various categories—there are 5 within the CCABADP—2 of the 3 categories contain GRASE active ingredients, their indications and various conditions for use, such as labeling and delivery systems. The 52 monographs are divided into three categories: final, negative and pending. The negative monograph contains categories for which there are no GRASE active ingredients.

New products that fit into one of the 26 final monographs can be sold without prior FDA approval as long as the new product adheres to the standards for labeling, etc., of that monograph and its particular category. The product and the active ingredient are then automatically considered GRASE without the company having to submit any tests or applications to the agency. If the FDA receives evidence of safety problems, or wants to make a change in labeling, for example, it must go through a laborious, 3-step rulemaking process to “amend” the monograph or eliminate the GRASE designation, which is the kiss of death for a product.

The 16 negative monographs contain no active ingredients that have been designated GRASE. However, a product in that category can be approved if the company marketing it submits a new drug application (NDA), and that application is approved. An example is Rogaine, which fits into the negative monograph category of “hair growers”—an OTC monograph category without any products until Rogaine was approved via an NDA. The same is true for Zovirax, a product for cold sores and blisters. These “NDA” products are considered outside the monograph system.

The pending monographs contain most of the “unsettled” product categories such as internal analgesics and topical antimicrobials—“unsettled” meaning that a GRASE decision is pending. In some instances, the manufacturer has submitted safety studies and the FDA has not had a chance to look at those studies because of staffing shortages. But it is a tricky category. For example, aspirin is GRASE for internal analgesics but not for external analgesics or as a sleep aid.

In some instances, the FDA can take decades to amend a monograph, which it must do via a lengthy rulemaking. That has been the case with acetaminophen, where the industry wanted to add a label regarding rare but serious events with skin allergies. The FDA has put out guidance but has never issued a final rule.

But questions remain about the status of final monograph products, too. The final (finalized in 1990) CCABADP monograph has 5 separate product categories: antihistamines (13 active ingredients), decongestants (13 active ingredients), antitussives (10 active ingredients), bronchodilators (7 active ingredients), and expectorants (1 active ingredient). For example, the FDA’s web page (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-the-CounterOTCDrugs/StatusofOTCRulemakings/ucm071141.htm) for nasal decongestants contains unfinished regulatory actions regarding numerous products. Other monographs, such as those for internal analgesics, sunscreens, and antimicrobials also have unfinished regulatory dockets.

But the FDA can move against those actives in the final category, too—and did in the case of phenylpropanolamine (PPA). The agency issued a public health advisory against the use of the drug in November 2000. In an advisory, the FDA requested that all drug companies discontinue marketing products containing PPA. As a result, retailers pressured manufacturers to discontinue sale of those products. In December 2005, the FDA issued a notice of proposed rulemaking for OTC nasal decongestant and weight control products containing phenylpropanolamine preparations, reclassifying phenylpropanolamine as non-monograph (Category II/negative), not GRASE.

But the FDA’s inability to make changes to pediatric cough and cold products is particularly galling to some who cite a 2007 petition written by Sharfstein and signed by others and, perhaps more importantly, votes taken by an FDA advisory committee in that same year. The petition requested that the following actions be taken: 1) creating labeling stating that cough and cold products are not to be used in children younger than 6 years of age; 2) issuing some sort of statement that these products have not been found to be safe or effective for the treatment of cough and cold in children under 6 years of age; 3) notifying manufacturers about products whose labeling uses such terms as “infant” or “baby” that such marketing is not supported by scientific evidence and that manufacturers will be subject to enforcement action.

The discussion at the advisory committee meeting in 2007 addressed a variety of issues, including the extrapolation of efficacy data from adults to children of any age for cough and cold products; the safety profile of these products in children; the basis for labeling recommendations in the CCABADP monograph and the use of pharmacokinetic data to determine appropriate dosing in children; the basis of dosing recommendations for various age groups including patients younger than 2 years of age, ages 2 to 5 years and 6 to 11 years; the use of the products in children younger than 2 years of age; the potential for misuse, unintentional overdose, and excessive dosing; the ability (or inability) of parents or caregivers to correctly dose and administer cough and cold products to their children; and the labeling changes recommended by the petitioner and the effects they would have on the use of these products in children and the recommendations of health care providers.

The advisory committee also voted 13 to 9 to recommend that pediatric cough and cold drugs should not be used for children under 6 years of age while rulemaking proceeded and voted 15 to 7 to recommend that the products should continue, for the time being, to be sold for use in children ages 6 to 11 while new studies are conducted.

But as of September 2018, the FDA has still not completed the monograph rulemaking it started in 2007, nor has the agency required new labeling for any products in the cough/
cold category, much less deemed any of the active ingredients unsafe and/or ineffective. However, in 2008, consumer OTC manufacturers voluntarily stopped marketing cough and cold products to children under 4 years old. That is done via language in the product’s labeling—which states “do not use” for children under 4—and eliminating pictures of young children or use of the word “infant” on product labels and packaging. However, the packages and cough/cold products contain no warning label, and according to some studies, parents still give the products to young children.

The Problem With the FDA

The FDA’s failure to amend the CCABADP and other monographs for products and active ingredients explains why Congress is on the cusp of approving a user fee for OTC products. On May 9, 2018, the House Energy and Commerce Committee approved H.R. 5333, the Over-the-Counter Monograph Safety, Innovation, and Reform Act of 2018, bipartisan legislation sponsored by Representatives Bob Latta (R-OH) and Diana DeGette (D-CO). On April 24, 2018, the Senate Health, Education, Labor and Pensions (HELP) Committee approved its companion bill, S. 2315, by a 22–1 vote.

“OTC Monograph reform will create a modern regulatory system for the modern OTC marketplace,” said CHPA’s Melville. “Now that both the Senate HELP Committee and House Energy and Commerce Committee have advanced legislation, we are optimistic that OTC Monograph reform will cross the finish line this year.”

Like the user fees already in effect for prescription, generic and biosimilar drugs, the OTC user fees would be paid by industry companies allowing the FDA to hire additional staff who could work on completing rulemakings like the one started in 2007 on cough and cold products. The current small OTC staff, funded only via Congressional appropriation, and a small one at that, has been solely dedicated to 3 areas in the last 4 fiscal years:

- statutory requirements of the Sunscreen Innovation Act;
- court-mandated requirements of the consent decree pertaining to antiseptic drug products; and
- urgent safety activities.

So it has been impossible for the staff to review data on monographs whose active ingredients and products require attention to questions raised by scientific evaluations or negative health effects seen in various database reports. The Congressional legislation would alter the FDA’s authority to allow it to use an administrative order to change a monograph instead of having to go through the 3-stage regulatory process to which it must now adhere. Industry would be provided a more streamlined regulatory pathway for review of innovations within the OTC Monograph system.

User Fees Badly Needed

Despite there being far more OTC products than branded drugs, the FDA's OTC budget is woeful compared to its budget for branded drugs. For comparison, the Congressional appropriation for prescription drugs in fiscal 2016, based on Woodcock’s testimony in 2017, was $320.9 million versus $7.9 million for OTC products. Prescription Drug User Fee Act (PDUFA) fees amounted to $836.9 million for a total FDA prescription drug regulatory program of $1.16 billion. There were no OTC user fees then or now, and the $22 million that Congress wants to approve for a first year OTC user fee supplement won’t go very far in closing the OTC versus branded gap with regard to FDA funding. However, the money would enable the FDA to hire about 100 new OTC employees over the 5-year period for the first user fee agreement.

Potential benefits of OTC Monograph reform with supporting user fees include:

- timely determination on the conditions for GRASE;
- ability to address safety issues in a more timely and efficient manner;
- ability to consider certain OTC product innovations proposed by industry;
- streamlined ability to update monographs to provide for modern testing methods that can improve the effectiveness of products available to consumers;
- development of information technology infrastructure for submission, review and archiving of monograph information;
- development of a modern, useful, transparent Web interface; and
- increased ability to respond to monograph-related concerns from the public and industry.

The Congressional reform legislation likely to pass this year would allow product sponsors to submit data packages to the FDA with requests that the FDA issue an administrative order for a change to a monograph. In addition, the FDA would commit to compressed timelines for certain kinds of innovative products for which a company would submit what is called an Innovation Over-the-Counter Monograph Order Request (OMOR). The FDA would commit to approving requests that meet certain conditions within 17.5 months. Examples of these would be:

- the addition of a new ingredient to a monograph that already has one or more ingredients that have been found to be GRASE;
- the addition of a new indication to a monograph that already has one or more ingredients that have been found to be GRASE, and the new indication applies to one or more of the GRASE ingredients;
- the addition of a new fixed-dose combination of ingredients to a monograph that already has one or more ingredients that have been designated GRASE.

The CPHA wants to be able to have a monograph quickly amended, which isn’t possible now, so that it can bring to market quickly, for example, products that contain active ingredients from 2 different monographs or a product with a new dosage form, particularly one that might have some public health benefits, such as a form of acetaminophen in a film that dissolves on the tongue, which would be a benefit to people who can’t take pills.

The new fees could also be used to advance lagging rulemaking...

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makings, such as one for the monograph for topical antimicrobial drugs, which would cover a wide range of hand-washing products intended for health care professional and consumer use. That rulemaking was in process for some time in part because scientists discovered that triclosan, an antibacterial substance commonly added to personal care products, was absorbed into the bloodstream more easily than previously thought and could impair muscle function. In the 1990s, the FDA began publishing several iterations of proposed rules (or tentative final monographs) covering product categories ranging from first-aid antiseptics to consumer hand-washes and sanitizers. In September 2016, it published a final rule covering only “consumer antiseptic washes” that effectively determined that triclosan and 18 other chemicals were unsafe—42 years after the process had started. The FDA still hasn’t published a monograph for all OTC topical antimicrobial products.

While the FDA has struggled to make amendments to monograph products and active ingredients, it has published consumer warnings and held public workshops to gather data. In 2013, the FDA published a drug safety communication alerting the public to serious skin reactions with acetaminophen. “Although these non-rulemaking approaches have been helpful as alternative ways to effect safety labeling changes and to notify consumers of safety concerns, these approaches are far from optimal because they do not result in changing the relevant monograph to reflect the new safety labeling,” Woodcock explained at the Congressional hearings in September 2017.

Clearly, the FDA can use the extra millions that user fees would supply. But given the depth of the hole that the agency’s OTC review program is in, Congress will be approving a shovel—$22 million in the first year and not much more in successive years—when the agency needs the equivalent of a front loader.