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October 6, 2016

Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Comments on Over-the-Counter Monograph User Fees
Docket No. FDA-2016-N-1092

Dear Sir or Madam:

Thank you for the opportunity to offer comments on the Food and Drug Administration (FDA) proposal to establish a user fee program to support timely and efficient FDA review of the efficacy and safety of ingredients included, or proposed for inclusion, in over-the-counter (OTC) monographs.

Pew is an independent, nonpartisan research and policy organization with a longstanding focus on drug quality and safety**.** Pew's current efforts include an initiative to improve the safety of OTC drug products.

OTC Drug Monograph System

OTC drug products include a wide range of commonly used therapies, such as pain relievers, cold medicines, creams and ointments. There are over 300,000 unique OTC drug products that include an estimated 800 active ingredients available for purchase today.[1] The market for OTC drugs is large and increasing. Retail sales of these products reached $32 billion last year, more than doubling in less than a decade.[2]

A prescription drug may be marketed after FDA reviewers evaluate and approve a sponsor's application. In contrast, most OTC drugs can be marketed without pre-approval if they comply with the relevant OTC drug monograph. While the FDA has the authority to approve or require updates to the label of a prescription drug in response to new safety information, making these changes for an OTC drug product involves a rulemaking and review process that frequently goes all the way to the White House.

A monograph is a regulatory standard that is published as a rule for different therapeutic categories of OTC drugs. Under the current framework, each active ingredient is placed, at the proposed rule stage, into one of three categories:

[1] Woodcock J. Modernizing The Other Side Of The Counter: FDA Oversight Of Nonprescription Drugs. *Health Affairs Blog.* 2016. http://healthaffairs.org/blog/2016/06/09/modernizing-the-other-side-of-the-counter-fda-oversight-of-nonprescription-drugs/. Accessed September 16, 2016.

[2] OTC Retail Sales 1964-2015. Consumer Healthcare Products Association website. http://www.chpa.org/PR_OTCRetailSales.aspx. Accessed September 16, 2016.

- I – ingredients that are generally recognized as safe and effective (GRASE), which become part of the detailed final monograph for the relevant product category;
- II – ingredients that are not GRASE, which will not be in the final monograph (but which can be marketed until the monograph is finalized); and
- III – ingredients for which there is insufficient information to determine whether they are GRASE (but which can be marketed until the monograph is finalized).

The monograph identifies which ingredients may be marketed and under what conditions. It includes details such as the acceptable dosage forms and how it should be labeled to provide appropriate instructions, uses, and warnings to consumers. If a sponsor follows the monograph exactly, it may market an OTC drug without prior FDA approval.

Challenges to Ensuring the Safety and Effectiveness of OTC Drug Products

There are four key challenges with the current system:

- Rulemaking is an inefficient and inappropriate method for drug regulation
- FDA is unable to respond to safety concerns in a timely way
- There is no mechanism to resolve FDA concerns about drugs for which there is inadequate data
- FDA's Non-Prescription Drugs Division lacks the resources to effectively oversee all OTC drugs

*Rulemaking is an inefficient and inappropriate method for drug regulation***.** The current process for finalizing and updating monographs is exceedingly inefficient and hampers FDA's effectiveness in regulating OTC drug products. In order to finalize the category into which each ingredient is placed and establish the other marketing conditions in the monograph FDA must follow a three-step rulemaking procedure, including public comment: the advanced notice of proposed rulemaking, the tentative final monograph, and the final monograph. Because it is a rulemaking, not a decision where FDA has the final authority, a monograph change is subject to an economic analysis; it is not purely a scientific decision. In contrast, the relevant review division at FDA can typically make decisions about the marketing conditions for prescription products, so the process for often higher-risk prescription products is significantly more streamlined than the process for over-the counter drugs. As a result of this process, there are 11 pending OTC drug monographs (of the original 26, some of which have since been subdivided) that FDA has still not finalized. In addition, even very basic changes and serious safety updates to the monograph can take many years. This also hinders innovation that could benefit consumers, such as the introduction of products with new ingredients, dose forms or ingredient combinations.

FDA is unable to respond to safety and effectiveness concerns in a timely way. The cumbersome process for updating monographs has public health consequences. For example, the FDA has been unable to require changes to the labels of cough and cold medications to address safety issues related to their use in young children. The Centers for Disease Control and Prevention estimated that there were more than 1500 emergency room visits in a 24-month period for children under two who had been given cough or cold products.[3] The lack of adequate safety information for their use in children was confirmed by FDA's Pediatric Committee and the Nonprescription Drug Advisory Committee in 2007 after an FDA review of the evidence, which found that OTC cough and cold products were linked to 123 deaths in children

[3] Centers for Disease Control and Prevention. Infant deaths associated with cough and cold medications — two states, 2005. MMWR 2007;56:1-4.

under six.[4] This expert advisory committee recommended immediate action against the use of cough and cold medications in children under six,[5] but almost a decade later there have been no changes to the monograph to reflect these safety concerns. Instead, FDA had to rely on voluntary action by manufacturers to stop labeling the products for children under two, and, eventually, to re-label them to recommend against use in children under four. In another example, decades of adverse event reports and an epidemiologic case-control study on phenylpropanolamine, an OTC nasal decongestant and weight loss drug, found that its use was associated with increased risk of hemorrhagic stroke. In 2000, a review by FDA's Nonprescription Drugs Advisory Committee concluded that phenylpropanolamine cannot be considered safe for continued use. The agency proposed classifying phenylpropanolamine as a Category II (non-monograph) ingredient in 2005,[6] but the relevant monographs have yet to be finalized. While manufacturers voluntarily halted sales of phenylpropanolamine products in response to FDA's safety concerns, the absence of a final regulation means a company could still legally market the drug. FDA does not the face the same challenges in responding to safety concerns for prescription drugs, for which the FDA has the authority to both approve and modify the marketing conditions in response to new information in a much more efficient manner than rulemaking.

The mechanism to resolve FDA concerns about drugs for which there is inadequate data is inefficient. When determining the monograph status of an ingredient, FDA must complete a laborious and resource-intensive process to locate and organize any evidence that may support its evaluation of an ingredient. And, because manufacturers have little incentive to submit unfavorable information about their products, FDA may also need to review the medical literature or commission independent research to develop a more complete understanding of the safety and effectiveness of an ingredient. Thus FDA's process for evaluating the evidence about an ingredient typically includes searching a large number of public comments submitted to the federal docket over many years that often include dated and unorganized information, as well as completing its own search of the medical literature, and then collating that information into a form that permits meaningful review. Drug information does not have to be submitted to FDA in any particular format, making the process of culling useful information extremely-time consuming. If the FDA concludes that it has inadequate information to make a GRASE determination about an ingredient, it issues a proposed rule outlining the evidence gaps for that ingredient. In response, stakeholders may submit additional material to the docket, again in no standardized format, thus restarting FDA's process of needing to synthesize all the available information. Only after completing this process, if FDA determines the evidence is still inadequate to determine an ingredient to be GRASE, can the agency pursue a final rule to designate the ingredient as a non-monograph ingredient. Up until a final rule is issued, these OTC products remain on the market, despite the uncertainty about their safety and effectiveness.

FDA's Non-Prescription Drugs Division lacks the resources to effectively oversee all OTC drugs. Complicating the inefficient monograph process is the fact that FDA is under-resourced to effectively

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[4] Food and Drug Administration, Division of Drug Risk Evaluation. Nonprescription Drug Advisory Committee meeting: cold, cough, allergy, bronchodilator, antiasthmatic drug products for over-the-counter human use. 2007:29. memorandum. http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4323b1-02-FDA.pdf. Accessed September 16, 2016

[5] Sharfstein, JM, North M, Serwint J R. Over the counter but no longer under the radar—pediatric cough and cold medications. *New England Journal of Medicine*. 2007; 357(23): 2321-2324.

[6] Phenylpropanolamine-Containing Drug Products for Over-the-Counter Human Use; Tentative Final Monographs, 70 Fed. Reg. 75988 (Dec. 22, 2005).

oversee OTC drug products. FDA has about 30 full-time employees working with a budget of less than $10 million annually to regulate the entire OTC industry.[7] For context, it takes approximately 18 FTEs to review a single application to market a new prescription drug.[8] At the beginning of FY 2016 there were over 1000 FTEs working in FDA's Office of New Drugs.[9]

Recommendations

The decision-making process for OTC products should not be more cumbersome than is necessary to protect public health.

Federal rulemaking is not an effective mechanism for regulating OTC drugs. Finalizing and updating monographs should not jeopardize patient safety or prevent useful new OTC products from coming to market. Decisions about whether ingredients are safe and effective should be scientific decisions, and FDA should be the arbiter of whether the scientific evidence supports a monograph change.

FDA should be able to take prompt action to remove or restrict products with OTC ingredients for which it has safety concerns.

FDA does not have the ability to quickly address safety problems that emerge for OTC products, even in cases of obvious harm. The current regulatory framework, which only allows for FDA to address safety problems through the slow process of updating the relevant monograph, poses serious public health risks. FDA's authorities to respond to emerging safety concerns with OTC drugs should more closely align with its authorities to take swift action to ensure the safety of prescription drugs.

FDA should have an efficient mechanism to get the information needed to evaluate OTC ingredients.

FDA is unable to make safety and effectiveness determinations for many active ingredients due to the lack of adequate data. While the agency has a statutory obligation to ensure the safety and effectiveness of OTC drug products, it cannot fulfill that responsibility if products may continue to be legally marketed in the absence of adequate data.

FDA should have flexibility and resources to prioritize public health needs.

As noted above, FDA currently devotes about 30 employees to oversee some 800 ingredients and over 300,000 different OTC drug products. Mandates from Congress (regarding sunscreens) and the courts (regarding antibacterial soaps) have dominated the use of existing staff, leaving FDA little flexibility to prioritize emerging public health needs. FDA should have the staff to allow it to respond to pressing health needs in addition to congressional and judicial demands. To function efficiently, FDA needs increased resources.

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[7] User Fees and the Future of the OTC Monograph System. FDA/CBER SBIA Chronicles. 2016,http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/UCM510074.pdf. Accessed October 6, 2016.

[8] Ibid.

[9] John Jenkins, CDER New Drug Review: 2015 update, presentation to FDA/CMS Summit (Dec. 14, 2015), http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM477020.pdf. Accessed October 6, 2016.

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An efficient process for approving and updating OTC monographs, coupled with adequate resources, would benefit public health by allowing FDA to respond to safety concerns and by facilitating the path to market for new innovations.

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