CHPA

founded 1881

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Comments of the Consumer Healthcare Products Association in Response to the Notice of Hearing on the Over-the-Counter Drug Monograph System (Docket No. FDA-2014-N-0202)

I. Introduction

The Consumer Healthcare Products Association (CHPA) is pleased to submit these comments in response to FDA's Notice of Public Hearing and Request for Comments on the Over-the-Counter Drug Monograph System—Past, Present, and Future, Docket No. FDA-2014-N-0202 (Notice).[1]

CHPA, founded in 1881, is the national trade association representing manufacturers and distributors of over-the-counter (OTC) or nonprescription medicines and dietary supplements in the United States. Our members make drugs covered by Over-the-Counter Drug Review (OTC Drug Review or the Review) monographs as well as products subject to abbreviated new drug applications (ANDAs) and new drug applications (NDAs). As such, we have an interest in the subject matter of the Notice.

CHPA applauds and is strongly supportive of FDA's re-examination of the monograph system in an effort to complete the OTC Drug Review. CHPA also strongly supports FDA's efforts to modernize the monograph system to respond more efficiently to new technology and emerging public health and safety concerns. CHPA believes that these objectives can be accomplished most effectively and efficiently by utilizing and reforming mechanisms that FDA already has in place. First and foremost, this entails the completion of rulemaking proceedings on the remaining tentative final monographs (TFMs). FDA will find that industry is anxious to engage in a collaborative and transparent dialogue to determine what remains to be done and to assist FDA by providing any additional data industry has available or may otherwise obtain to accomplish this goal.

However, finalizing the monographs does not mean that they should remain static documents that do not change in response to advances in science and medicine, and new information concerning safety. CHPA supports, and is willing to be FDA's partner in, the establishment of mechanisms to respond to such developments and to improve OTC drug

[1] 79 Fed. Reg. 10168 (Feb. 24, 2014).

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regulation in the future. Therefore, we suggest changes in the existing procedures, such as improving the time and extent application (TEA) process and streamlining procedures for permitting changes in products covered by final monographs. In addition, as was true with the OTC Drug Review from its beginning, CHPA believes that appropriate use of FDA's enforcement discretion will be a critical tool to proceeding expeditiously and responding to emergent issues.

II. General Background and Comments on the Monograph System

The OTC monograph system has served FDA, consumers, and industry well over the last forty years. The system has strong foundations in the OTC Drug Review itself, which was the largest regulatory undertaking in the history of FDA and one of the most successful. CHPA believes that if FDA returns to the origins of the OTC Drug Review and examines the bases for its early success, the remaining monographs can be completed and updated, and the system can continue to serve stakeholders as well as, if not better than, it has in the past.

The task facing FDA at the outset of the OTC Drug Review was, if anything, more difficult than the job that remains to be done today. When the OTC Drug Review began, FDA confronted a choice between conducting tens of thousands of reviews of specific products and potentially initiating litigation or administrative proceedings concerning them, or devising a more efficient and comprehensive solution. Many of these products contained the same active ingredients and indications and had been on the market for decades. They had a long history of safe use and played an important role in healthcare, but they had not been reviewed according to the standard for effectiveness set forth in the 1962 Drug Amendments. The OTC Drug Review permitted these products to remain on the market while FDA determined whether they met standards for general recognition of safety and effectiveness.[2]

The Review also solved two additional problems. First, it avoided the substantial expenditure of resources that would have been necessary to review each drug individually, a task which the Commissioner determined to be "cumbersome, time consuming and confusing."[3] Second, it avoided inevitable inequities between manufacturers that would result if a drug-by-drug approach were adopted. Simply stated, proceeding drug-by-drug would give an unfair

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[2] In using the term "monographs," CHPA is referring to Parts within Title 21 of the Code of Federal Regulations. These Parts pertain to therapeutic categories of OTC drugs (*e.g.*, antacids, laxatives) and to Subparts covering therapeutic categories of OTC drugs (*e.g.*, first aid antibiotics, topical antifungals, topical acne). This definition includes negative monographs, or circumstances in which FDA concluded there were no ingredients generally recognized as safe and effective in the therapeutic category, and any drug so marketed would be a new drug (*e.g.*, smoking deterrents). We recognize the OTC Drug Review process has also included rules specific to individual ingredients or claims, which we do not refer to as monographs in these comments.

[3] 37 Fed. Reg. 9464, 9465 (May 11, 1972).

competitive advantage to the drugs that remained on the market, while their competitors were removed from the market as FDA arbitrarily proceeded from product to product.[4]

The basic premise of the Review was an exercise of enforcement discretion, under which FDA permitted OTC drugs to remain on the market pending decisions in the Review. In addition, the "rush-to-market rule," finalized in 1976, permitted prompt introduction of new OTC products containing active ingredients or dosages previously restricted to prescription use, provided they were classified as Category I in proposed or tentative final monographs, thereby significantly broadening the range of effective treatments available for self-medication.[5]

To carry out the Review, FDA established an efficient and fair process for obtaining the published and unpublished literature and data that industry and other stakeholders had available at the time and evaluating that data to determine the safety and effectiveness of the relevant products.[6] Stakeholders were given several opportunities to present relevant data -- first to expert review panels and later in response to proposed and tentative final monographs. The resulting process was enormously successful and enjoyed broad support inside and outside of the Agency: FDA received over 20,000 volumes of data, upon which the expert panels relied to produce comprehensive reports on each active ingredient.[7] Those reports, taken together with comments submitted by stakeholders and reviews conducted by FDA, formed the basis for the current monographs.[8] The process was, moreover, highly efficient. The first final monograph, for OTC antacid products, was issued only two years after beginning the Review.[9]

III. Responses to Individual Questions

1. What aspects of the OTC Drug Review continue to function effectively?

CHPA members believe that the monograph system has served FDA and stakeholders well and that it can and should continue to serve as the cornerstone of OTC drug regulation. The OTC monograph system has brought order to the regulation of hundreds of thousands of OTC products according to sound scientific principles. The monographs are based upon an accumulation of 20,000 volumes of publicly available data that was submitted to FDA over the course of the OTC Drug Review.[10]

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[4] *Id.*

[5] 41 Fed. Reg. 32580 (Aug. 4, 1976).

[6] 37 Fed. Reg. at 9473-74.

[7] PETER BARTON HUTT, ET AL., FOOD AND DRUG LAW, CASES AND MATERIALS 979 (2014); Kenneth C. Baumgartner, *A Historical Examination of the FDA's Review of the Safety and Effectiveness of Over-the-Counter Drugs*, 43 FOOD & DRUG L. J. 463, 474 (1988).

[8] *Id.* at 474-76.

[9] 39 Fed. Reg. 19862 (June 4, 1974).

[10] PETER BARTON HUTT, ET AL., FOOD AND DRUG LAW, CASES AND MATERIALS at 979.

The review process also led to monographs covering established products and ingredients that enjoyed and still enjoy a wide margin of safety. Moreover, ingredients as to which there was not well-established safety and a reasonable assurance of effectiveness were removed from the market prior to or during the Review, including approximately 500 ingredients that were not determined to be generally recognized as safe and effective. In short, the OTC Drug Review has worked well, and it has accomplished much of what was intended.

(i) *Numerous Legislative and Regulatory Updates to the System Supplement the Regulatory Framework in the Monographs*

The regulatory system for OTC drug products is not, however, limited to the OTC review process. Instead, it consists of a comprehensive series of controls that assure the safety and quality of all OTC drug products. Relevant controls include, for example, requirements for compliance with current good manufacturing practice (cGMP) as well as monographs contained in the United States Pharmacopeia and National Formulary (USP/NF) that establish detailed requirements for the purity of active and inactive ingredients and for certain finished formulations.[11] In 1997, Congress gave FDA the same authority for records inspection for OTC drugs that it has for prescription drugs, and required that OTC drug labels declare inactive as well as active ingredients.[12] Manufacturers of OTC drug products must register with FDA and submit periodic lists of their products, and they are subject to regular inspections by the Agency.[13]

Under regulations issued in 1999, OTC drug products bear "drug facts" labeling, setting out required information in an easy to understand format for consumers.[14] In 2007, Congress required mandatory adverse event reporting for OTC drugs not subject to NDAs or ANDAs.[15] FDA guidance requires manufacturers to maintain robust systems to track all adverse events and product complaints.[16]

(ii) *The Partnership Between Stakeholders and FDA has Pushed New Changes Forward*

The monograph system has also promoted a cooperative relationship between stakeholders and the FDA. Industry frequently responds voluntarily to emerging safety concerns even before the notice and comment rulemaking process produces an official change. Numerous examples show that stakeholders have strong incentives to respond to new data and information

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[11] USP, *USP Monographs Fact Sheet*, *available at* http://bit.ly/1hzVE7T.

[12] 111 Stat. 2296 (1997), 21 U.S.C.§§ 352, 374, FD&CA §§ 704(a)(1), 502 (e)(1).

[13] 21 U.S.C. § 360.

[14] 21 C.F.R. § 201.66; 64 Fed. Reg. 13254 (Mar. 17, 1999).

[15] 21 U.S.C. § 706.

[16] FDA, Guidance for Industry: Post-marketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed Without an Approved Application (July 2009).

regarding safety, whether derived from studies conducted by industry or communications from FDA.

One example is phenylpropanolamine hydrochloride (PPA). Following reports of hemorrhagic stroke in persons using PPA, FDA asked industry to conduct a safety study, which was promptly undertaken. However following results of the study, which showed a small increase in the risk of stroke in women taking PPA, an FDA advisory panel recommended against continued marketing of the ingredient. Manufacturers voluntarily withdrew PPA from the market as early as 2000, well before FDA issued a notice of proposed rulemaking to classify it as a Category II or non-monograph ingredient in 2005.[17]

Danthron, an active ingredient used in laxative products, provides another example. In January 1987, a leading U.S. manufacturer of laxative products informed FDA that it would voluntarily cease distribution of laxative products containing the ingredient, based in part on studies conducted in the United Kingdom and Japan suggesting that it increased the risk of tumors in rats. In March of 1987, at FDA's request, manufacturers and distributors of danthron-containing products initiated voluntary recalls.[18] Ten years later in 1997, FDA proposed to amend the laxatives monograph to re-classify danthron as a Category II or non-monograph ingredient,[19] and in January of 1999 FDA issued a final rule.[20]

Under a voluntary program adopted by the CHPA Board of Directors in 2008, manufacturers of OTC oral pediatric cough and cold medicines made a series of changes to enhance safe use of these medicines, including labeling that directs against use in children under age 4 and adoption of child-resistant packaging for all OTC medicines labeled for use in children under age 12.

More recently, in 2012, manufacturers voluntarily standardized pediatric liquid dosage forms of acetaminophen for infants and children to a single concentration of 160 mg/5 mL, consistent with an FDA advisory committee recommendation. This change eliminated at least two other formulations from the market, which reduced the potential for consumer confusion.

(iii) *Stakeholders Continue to Provide Data and Studies to Update the Review*

Industry has been willing to provide available data to support FDA's decisions on new technology and safety issues. For example, CHPA members conducted a randomized, double-blind, placebo-controlled pivotal trial that evaluated the safety and effectiveness of benzocaine gel (10% and 20%) for the relief of toothache pain and user compliance with dosing directions. Results from this study, which were published in the Journal of the American Dental

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[17] 65 Fed. Reg. 52775 (Aug. 30, 2000).

[18] FDA, *For Immediate Release* (Mar. 30, 1987), *available at* http://1.usa.gov/1hsPdDx.

[19] 62 Fed. Reg. 46223 (Sept. 2, 1997).

[20] 64 Fed. Reg. 4535 (Jan. 29, 1999).

Association in 2013,[21] support the classification of topically applied benzocaine as generally recognized as safe and effective for the temporary relief of toothache pain in the final monograph for OTC Oral Healthcare Drug Products.

CHPA members conducted a series of safety studies, including skin penetration, tumor promotion with ultraviolet initiation, animal carcinogenicity and photocarcinogenicity of benzoyl peroxide. CHPA members also sponsored a retrospective case-control epidemiology study that found acne treatments containing benzoyl peroxide were not a risk factor for facial skin cancers. These data supported classification of benzoyl peroxide as generally recognized as safe and effective in the monograph for OTC topical acne drug products in 2010.[22]

CHPA members have also provided data to FDA supporting *in vitro* test methods for anticaries performance testing, validated against the monograph-required rat caries test method. Feedback from FDA is needed on remaining data gaps to facilitate acceptance of these methods. The industry is willing to discuss further studies if needed, but it would first want to understand FDA's conclusions concerning the existing data and any additional information it requires to make a final decision on the acceptability of these methods.

2. <u>Which aspects of the OTC Drug Review are most in need of change?</u>

The aspects of the Review that are most in need of change are accelerating the completion of the final monographs, swiftly addressing urgent safety issues, and identifying an efficient and effective process to amend final monographs, including the addition of new ingredients. In each instance, industry needs more information in order to be helpful. The rulemaking process is not transparent, and industry therefore does not have access to precise information concerning the status of the relevant rulemakings. CHPA therefore urges FDA to establish a system under which the status of each rulemaking can be readily determined by all interested persons.

CHPA recommends that FDA improve its procedures for communicating with stakeholders concerning the issues that remain outstanding in each rulemaking and the data that the Agency needs to resolve those issues. Specific improvements could include one or more public meetings to discuss the status of the review process, along with establishment of an up-to-date website containing detailed information on the status of each monograph. Websites that provide possible models include the FDA Drug Supply Chain Security Act actions tracking site[23] and the Office of Information and Regulatory Affairs (OIRA) clearance site.[24] We suggest that a

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[21] Hersh, E.V., et. al., JADA 144(5): 517-526 (2013).

[22] 75 Fed. Reg. 9767 (Mar. 4, 2010).

[23] FDA, *Drug Supply Chain Security Act Implementation Plan, available at* http://www.fda.gov/Drugs/DrugSafety/DrugIntegrityandSupplyChainSecurity/DrugSupplyChainSecurityAct/ucm382022.htm.

[24] OIRA, *Regulatory Review Dashboard, available at* http://www.reginfo.gov/public/jsp/EO/eoDashboard.jsp.

similarly comprehensive website be established to set forth the status of each monograph and a checklist of action items.

FDA should work to revive the distinction between the scientific evidence necessary to support a determination of general recognition of safety and effectiveness and the evidence necessary for an NDA. As was understood during the original OTC Drug Review process, the determination of general recognition of safety and effectiveness depends in large part on publicly available scientific literature, rather than the original clinical study reports that ordinarily support NDAs.[25] In finalizing its procedures for the Review, FDA stated that the "panel's evaluation of a drug should be based on the best scientific evidence available. In most cases, this consists of published studies which are available for peer review and criticism."[26] Regarding this point, FDA should also take account of experience with the procedure for approval of "paper-NDAs," which was ratified by the courts in the 1980s.[27] As with the OTC Drug Review, the "paper NDA" procedure permitted reliance on "reports in scientific literature to establish the drug's safety and effectiveness."[28]

3. **Are there additional mechanisms to eligibility for the OTC Drug Review that could be explored? If so, what should be the parameters of eligibility?**

CHPA urges FDA to streamline the time and extent application (TEAs) system to make it a more effective tool for including new active ingredients in the OTC review process. The existing procedure is inadequate to serve its intended purpose: after more than 11 years, not a single active ingredient has been permitted for use under the TEA procedure. As a result, U.S. consumers have been denied access to safe and effective active ingredients, including sunscreen ingredients, that have long been available in Europe and elsewhere around the world.[29]

As CHPA has noted in prior submissions to the Agency, the current procedure is unduly complex. It entails three rounds of submissions: (1) an eligibility determination requiring significant data, (2) a subsequent safety and efficacy data submission, and (3) a notice and comment rulemaking to amend the monograph.[30] During the first two stages of this process,

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[25] 37 Fed. Reg. at 9467-69.

[26] *Id.* at 9469. *See also* 21 C.F.R. § 330.10 (a)(4)(i) ("General recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data."); 21 C.F.R. § 330.10(a)(4) (ii) (same for effectiveness).

[27] *See, e.g.*, Burroughs Welcome v. Schweiker, et al., 649 F.2d 221, 225-26 (4th Cir. 1981); *see also* Upjohn Manufacturing Co. v Schweiker, et al., 681 F.2d 480 (6th Cir. 1982).

[28] 649 F.2d at 223.

[29] 67 Fed. Reg. 3060 (Jan. 23, 2002); FDA, *Guidance for Industry: Time and Extent Applications for Nonprescription Drug Products* (Sept. 2011).

[30] 21 C.F.R. § 330.14 (c)-(g).

the applicant is required to make substantial submissions, with no assurance that the ingredient will proceed to the third stage, much less to inclusion in a final monograph.[31]

CHPA believes that the process can be greatly simplified, permitting it to serve its intended purpose of allowing ingredients that have been demonstrated to be generally recognized as safe and effective through use abroad to enter the U.S. market. FDA should make two reforms. First, it should collapse the three steps into two and reduce redundant data requirements. Put differently, FDA should conduct a ***threshold*** review of eligibility with limited requirements, and then the FDA should move to a proposed rule and promptly call for the data necessary for general recognition of safety and effectiveness. Second, FDA should consider permitting ingredients that are accepted under the threshold eligibility review to be marketed on an interim basis, while an amendment to the monograph is pending.

For example, for ingredients such as sunscreens with a long history of safe use in Europe or other developed jurisdictions, a streamlined time and extent application process would consist of (1) FDA's determination that a petition contains sufficient information relating to extent of use and (2) issuance of a proposed rule to include the ingredient in the relevant monograph. The proposed rule would include a statement that the ingredient may be used in the interim while the rulemaking is conducted.

4. <u>Why is the NDA deviation process rarely used by industry? Are there changes to that process that would make it a more appealing and appropriate alternative pathway?</u>

CHPA suggests that industry has not used the procedure for three reasons. First, as implemented by FDA, the procedure does not appear to serve its intended purpose, which is to require an applicant to submit only the information needed to support the specific deviation from the relevant monograph.[32] In the one case where the procedure was used, FDA required submission of *in vitro* effectiveness studies as well as manufacturing information beyond what was needed to support the proposed deviation.[33] The Agency's approach was not consistent with

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[31] *Id.* § (c)-(f).

[32] 21 C.F.R. § 330.11.

[33] In 2000, the FDA approved a deviation from the monograph for OTC Pediculicide Drug Products for a new dosage form. Specifically, the monograph only permitted a non-aerosol dosage form, and the manufacturer wanted to market its lice treatment product in an aerosolized foam form. *Bayer Rid Pediculicide Marketing Begins with Mousse Launch*, TAN SHEET (June 26, 2000). The manufacturer submitted an application indicating that it otherwise met all of the conditions of the final monograph. It then submitted information from two *in vitro* studies related to the safety and effectiveness of the active ingredient, as well as new chemistry, manufacturing and control information. Medical Review for Application 21-043, *available at* http://1.usa.gov/1sxkMFm. The application was submitted in 1998 and was ultimately approved two years later in 2000. Approval Letter for Application No. 21-043 (Mar. 7, 2000), *available at* http://1.usa.gov/1jS0p1B.

the language of the NDA deviation provision, which expressly permits the applicant to "omit all information except that pertinent to the deviation."[34]

Second, because the NDA deviation was adopted prior to enactment of the Hatch-Waxman Act in 1984, it does not provide important regulatory incentives, such as patent linkage (*i.e.*, listing in the Orange Book) and non-patent regulatory exclusivity for changes that are required to be supported by clinical studies.[35]

Third, the NDA Deviation process requires that there be a final monograph. This further limits its usefulness because it prohibits its use with products marketed under the TFMs.[36]

For these reasons, deviations from a monograph that require safety and effectiveness data beyond those in an OTC drug monograph, are most appropriately made by means of an application under Section 505(b)(2) of the FD&CA. Use of this pathway for such changes is clearly consistent with the relevant FDA regulation.[37] For Section 505(b)(2) to be effective in this respect, FDA should narrowly tailor its data requirements to the precise change from the monograph. Specifically it will be important for FDA to ensure that review divisions do not require applicants to submit new data beyond what is necessary to demonstrate the safety and effectiveness of the proposed change from the conditions set out in the relevant monograph.

For new dosage forms or other changes that do not entail the need for new safety or effectiveness studies, FDA should issue guidance describing the data that manufacturers should maintain to demonstrate that finished products will comply with 21 C.F.R. 330.1(e), which establishes general requirements for the inactive ingredient formulations of monograph drug products.[38]

5. <u>Ideas for a streamlined process that would allow us to promptly resolve all TFMs?</u>

CHPA strongly urges FDA to adopt a comprehensive plan for finalizing the remaining TFMs. We see this process proceeding in several steps. First, we believe FDA should appoint a single leader with accountability for finishing this process. That leader should be outside of the Office of New Drugs and report directly to the Office of the Center Director, in order to maximize the focus on the unique characteristics of the OTC Drug Review and the pending rulemaking proceedings. Second, FDA should prioritize which monographs, or in some cases, subparts of monographs, should be completed first. Precedent exists for completing monographs in subparts, as was done with the cough and cold monograph.

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[34] 21 C.F.R. § 330.11.

[35] 21 U.S.C. §§ 355(j)(5)(F)(iii), (j)(7).

[36] *See* 21 C.F.R. § 330.11.

[37] FDA, *Guidance for Industry: Applications Covered by Section 505(b)(2)* 5 (Oct. 1999).

[38] *See* 21 C.F.R. § 330.1(e).

Third, FDA should instruct its reviewers to review data in a manner that is consistent with the statutory requirements for determining that drugs are generally recognized as safe and effective and not subject to the NDA requirement.[39] In developing guidance for reviewers in this respect, FDA should take account of past experience with the original OTC Drug Review and/or the procedure for approval of "paper-NDAs."

According to these priorities, FDA should establish milestones for completion of the monographs, with specific timeframes. As stated above, the process of completing the monographs would be enhanced if FDA would establish a website location setting forth these goals and measuring the progress toward each of them. OIRA's Regulatory Review Dashboard website may serve as an example in this respect. In addition, FDA should discuss the milestones and timelines with industry in a public meeting, and, at that time, FDA should issue a targeted call for the specific data needed to bring the monograph into final form. This request will make it more efficient for industry to respond with data that it may already have on file and/or to discuss with FDA how best to meet its needs. FDA might also consider establishing a more formal collaborative partnership with industry and other stakeholders or experts to collect and evaluate the available data, such as a public-private partnership. In the interim, FDA should rely on its enforcement discretion to respond to issues as they arise prior to the finalization of the monograph.

6. <u>Issue monographs by administrative order?</u>

CHPA does not believe that the procedure recently adopted for issuance of "administrative orders" to reclassify medical devices under the FDA Safety and Innovation Act (FDASIA) is well suited to the complex decisions required for the OTC Drug Review.[40] As noted above, the OTC Drug Review was an alternative to a drug-by-drug determination that each OTC drug and ingredient on the market is safe and effective. These determinations depend on findings that active ingredients and dosage forms are supported by the evidence required for general recognition of safety and effectiveness. The brief, conclusory explanatory statements that have accompanied reclassification orders under the FDASIA procedure would clearly not be sufficient to support final or amended monographs under the OTC Drug Review.

Nor will an administrative order or "adjudication" procedure relieve FDA of the extensive work associated with notice and comment rulemaking. Any decision that FDA makes, whether in an administrative order or a rule, will still be a "statement of general or particular applicability and future effect" to a class of drugs marketed under a monograph. It must therefore, still be explained in substantial detail, including responding to comments submitted, in

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[39] 37 Fed. Reg. at 9469; *see also* 21 C.F.R. § 330.10(a)(4)(i)-(ii).

[40] FDASIA, 126 Stat. 1055 § 608 (codified at 21 U.S.C. § 513(e) (2012)) (excepting administrative order from requirements of "subchapter II of chapter 5, title 5 of the United States Code").

order to survive judicial review.[41] If FDA fails to do this, an order may be set aside by a court under the relevant provisions of the Administrative Procedure Act.[42]

7. Issue regulations to require product specific information and expand the use of guidances?

CHPA strongly believes that the best use of FDA's rulemaking power is to finalize the existing TFMs. In addition, as noted above in III point 4, FDA should issue detailed guidance and discuss its expectations going forward. Having an open and transparent dialogue on this process will ensure cooperation.

8. Expand the NDA deviation process?

As noted above in III point 4, the enactment of Section 505(b)(2) into the FD&CA to a certain extent obviated the need for the NDA deviation process. Therefore, for changes requiring additional safety and effectiveness data, the Section 505(b)(2) pathway is most appropriate, as FDA itself has noted. In addition, for other changes a combination of guidance from FDA as well as new procedures from USP would permit both FDA and applicants to deal with these changes in a more expeditious way.

9. What alternatives or changes to the OTC Drug Review would modernize or improve FDA's regulation of monograph drugs?

In response to this question, CHPA would refer FDA to III points 3-5 above. CHPA strongly supports FDA taking those actions to modernize the OTC monograph system.

10. How can the Agency most expeditiously address emerging safety issues for drugs regulated under the OTC Drug Review?

CHPA believes that FDA already has ample authority to respond to emerging safety issues relating to products covered by the OTC Drug Review. As it has done in the past, FDA need only make its concerns clear as it does now, for example, via a Drug Safety Communication. Specifically, FDA should issue a Drug Safety Communication identifying specific labeling changes that are responsive to the safety concern and inform those responsible for marketing the product that they may make these changes on an interim basis, while a rulemaking is ongoing. Once FDA has done so, it will find the regulated industry willing to cooperate in adopting labeling changes, conducting studies or, when necessary, removing ingredients from marketed products well before formal rulemaking procedures are completed.

This approach to regulation is one that FDA has employed on numerous occasions, and the OTC industry has a consistent record of responding to the Agency's notices and communications. The OTC Drug Review itself was built on enforcement discretion, and many

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[41] 5 U.S.C. § 551(4).

[42] *See* 5 U.S.C. § 706.

examples exist in which industry has made changes to or withdrawn products in response to FDA's issuance of a notice on its website or in the Federal Register.[43]

Similarly, FDA should respond promptly when industry seeks its advice on the addition of new warnings or other measures to respond to emerging safety concerns. This prompt action is in accordance with FDA's mandate to protect human health and safety. The Agency has yet to respond to a citizen petition submitted by CHPA seeking enforcement discretion to include dosing information for children 6 months to 2 years of age in the labeling of acetaminophen products.[44] This change was unanimously recommended by an FDA advisory committee and could be made immediately, without waiting for rulemaking procedures.

In addition, when concerns arose regarding the possibility that benzocaine might be associated with methemoglobinemia,[45] industry asked FDA to exercise enforcement discretion to allow changes to warning statements in labeling. To date, the Agency has not responded to this request.

11. Are there specific changes to the OTC Drug Review that the Agency could employ to address the lack of pediatric data for some final monographs?

If FDA issues specific requests in a Federal Register notice, manufacturers will readily submit relevant data. If the required data do not already exist, FDA and industry can engage in a dialogue about how to best meet FDA's needs. CHPA has previously submitted reports of pediatric studies that it has sponsored, such as with the benzocaine study noted above, which involved both adults and adolescents.

CHPA has also sponsored new studies on pediatric cough cold products and shared the resulting data with FDA. The CHPA Pediatric Cough Cold Task Group is committed to increasing the body of evidence supporting the safety and effectiveness of cough and cold monograph ingredients in children. Members of the Task Group oversee a comprehensive research and education program initiated in 2008 and have made significant progress towards

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[43] In addition to the cases cited earlier in these comments, the industry's response to concerns about rare skin reactions reported with acetaminophen presents a recent example. Last year, FDA issued a Drug Safety Communication requiring NDA holders to include a warning on the package inserts for acetaminophen-containing products concerning those reactions. *FDA Drug Safety Communication: FDA warns of rare but serious skin reactions with the pain reliever/fever reducer acetaminophen* (Aug. 2013), *available at* http://1.usa.gov/1hmxJvL. CHPA members are responding to this notice by adding new warnings in the labeling for monograph products.

[44] CHPA, *Citizen Petition: Dosage Information for Children Aged Six Month to Two Years* (Aug. 15, 2013), *available at* http://www.chpa.org/08_15_13_CitizenPetitionPedAPAPLabels.aspx.

[45] FDA, *Drug Safety Communication: Reports of a rare, but serious and potentially fatal adverse effect with the use of over-the-counter (OTC) benzocaine gels and liquids applied to the gums or mouth* (Apr. 7, 2011), *available at* http://www.fda.gov/drugs/drugsafety/ucm250024.htm.

providing current scientific data related to the final monograph for Cold, Cough, Allergy, Bronchodilator, Antiasthmatic Drug Products for Over-the-Counter Human Use.[46]

The Task Group's comprehensive research program has included a five-year safety surveillance study, conducted by the Rocky Mountain Poison & Drug Center (Denver, CO). This program has shown that children's cough and cold medicines are safe when used as directed. Accidental, unsupervised ingestions at high doses are the leading cause of pediatric serious adverse events. A sustained education effort about proper use and storage of these medicines has been in place to improve safe use. A publication from the Center for Disease Control (CDC) shows that safe use has improved, by measuring a reduction in emergency department visits associated with these products. Clinical research in children continues, and has included pharmacokinetic studies on eight cough and cold ingredients, non-drug method development studies and efficacy research.

12. Should the only alternative to marketing an OTC drug under an OTC monograph be an NDA or abbreviated NDA approval? If not, what could another alternative be?

Most changes to monograph products can be accomplished through guidance documents or Section 505(b)(2) applications. Another option that FDA might wish to consider could be modeled on temporary use permits that the Agency issues for food products that do not conform to standards of identity.[47] These variances were issued to permit marketing of new products while FDA carries out the rulemaking process to amend the relevant standard of identity.[48] The system was established because of the recognition by FDA that the lengthy process for amending standards of identity could prevent innovation. For that reason, FDA has come to allow continuous marketing of the product during the standard amendment process.[49] Although a mechanism of this type would have to be adapted to suit the OTC drug regulation system, it illustrates one way in which a certain degree of flexibility from the monographs can be created to permit advances in science and technology, pending a formal amendment.

13. Are there other regulatory mechanisms (not necessarily used for the regulation of drug products) that are used by other agencies in the United States or in other countries that FDA could consider using to regulate OTC drugs products?

CHPA believes that the U.S. monograph system compares favorably to systems in other countries. The U.S. system is more open and transparent. At each stage of the process, the data and findings were explained in comprehensive panel reports and FDA preambles. In our

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[46] 21 C.F.R. § 341.

[47] 21 C.F.R. § 130.17.

[48] *Id.* § 130.17(a).

[49] *Id.* § 130.17(i). *See also* HUTT, ET AL., FOOD AND DRUG LAW, at 347 (noting that the Agency has liberalized the permits to accommodate continuous marketing during the pendency of standard amendments).

view, the U.S. monograph system is unique in comparison to other systems in its level of transparency and in the substantial data needed to meet the standard of general recognition of safety and effectiveness.

In the other countries with monograph systems that we examined, namely Canada and Australia, the relevant health agencies do not appear to subject the monographs to the same level of public scrutiny and data collection. For example, in Canada monographs and labeling standards are published online for commonly used products, *e.g.*, acne therapy, athlete's foot treatments, contact lens disinfectants, and throat lozenges. However, the monographs are short, conclusory documents, and unlike the volumes of data submitted in the U.S., these monographs appear to be based in substantial part on citations to secondary sources, often including monographs issued under the U.S. OTC Drug Review.[50]

The circumstances are similar in Australia, where the Therapeutic Goods Administration (TGA) initiated a 12-month pilot program for monographs for OTC medicines in October of 2013.[51] To date, the TGA has published three monographs, similar in form and content to the Canadian monographs, on oral use of aspirin tablets, ibuprofen, and paracetamol (acetaminophen). Neither of these systems would be suitable for use in the U.S. regulatory framework, which requires a detailed, science-based determination that ingredients meet the statutory standards for general recognition of safety and effectiveness.[52]

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[50] The Category IV monograph for throat lozenges posted on Health Canada's website is instructive. It is a four-page outline of parameters in various categories, covering similar topics to a U.S. monograph, including pharmaceutical quality, ingredients, labelling, dosage and warnings. Category IV Monograph, Throat Lozenges, *available at* http://bit.ly/1qf5aCC. The references section includes ten citations. Four citations are to general handbooks, and one citation is to a Health Canada advisory report, but five of the ten citations are to Federal Register documents issued under the OTC Drug Review. The Category IV Acne Therapy monograph also follows this pattern. It too is a four- page document, and of the six cited references, one is the USP/NF standard and the other is the FDA's monograph for Topical Anti-Microbial Products.

[51] Therapeutic Goods Administration (TGA), *OTC N2 Applications and OTC Monographs*, *available at* http://bit.ly/1ipJEYQ. The TGA posted various documentation related to the trial monograph program online for stakeholder comment and subsequently finalized three initial monographs after receiving five comments from stakeholders. TGA, *Outcome of Consultation: OTC N2 Application Requirements and OTC Medicine Monographs, available at* http://bit.ly/OszwVJ. The monographs that the TGA released are similar to the Canadian monographs described above, and therefore, FDA's monographs in terms of the level of detail and soundness of the conclusions would also compare very favorably. *See, e.g.*, OTC monograph: Aspirin Tablets for Oral Use, *available at* http://www.tga.gov.au/industry/otc-argom-otc-n2-monographs-aspirin.htm.

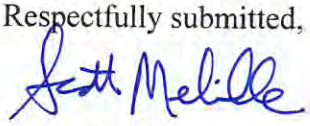
[52] Australia's system is also not based on a distinction between new drugs and old drugs, as was the OTC Drug Review. Rather, the application process for OTC medicines in Australia is determined according to the level of risk. The levels are defined as N1 to N5. For example, the lowest level of risk, an N1 application, is for a "clone" of a parent that has been fully evaluated (continued...)

IV. Conclusion

CHPA applauds and emphasizes its strong support for FDA's re-examination of the monograph system in an effort to complete the OTC Drug Review. We also strongly support FDA's efforts to modernize the monograph system to respond more efficiently to new technology and emerging public health and safety concerns. In this spirit, the association is ready and willing to engage in discussions to implement improvements to the current process.

Thank you for the opportunity to provide these comments to FDA. Should FDA have any questions or seek additional information, please do not hesitate to contact us.

Respectfully submitted,



Scott Melville
President and CEO
Consumer Healthcare Products Association

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for safety and efficacy for a flavor, fragrance or color variant meeting certain criteria. An "N2" application is the second level of risk for a drug that complies fully with an OTC Medicine Monograph. Sponsors must submit a "list of assurances" with their application that the product meets requirements.[52] TGA, *OTC Application Categorisation Framework, available at* http://www.tga.gov.au/industry/otc-tools-ac-framework.htm. Because of this structure, the Australian system is not helpful in providing analogous mechanisms for the challenges that the U.S. system faces, *i.e.*, updating the monographs governing old drugs and incorporating new drugs, ingredients, or dosage forms into that system.