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7272 Wisconsin Avenue  
Bethesda, Maryland 20814  
301-657-3000  
Fax: 301-664-8877  
www.ashp.org

March 13, 2014

Food and Drug Administration  
Office of the Commissioner  
Division of Dockets Management (HFA-305)  
5630 Fishers Lane  
Room 1061  
Rockville, MD 20852

**Re: Docket No. FDA-2013-N-0500, Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products**

Dear Sir/Madam:

The American Society of Health-System Pharmacists (ASHP) is pleased to submit comments to the Food and Drug Administration (FDA) on parity among labeling changes submitted by abbreviated new drug application (ANDA) holders. FDA's proposed rule would permit ANDA holders to distribute revised labeling in advance of FDA review for certain safety changes that would differ, on a temporary basis, from the labeling of its respective reference listed drug (RLD) as a "changes being effected" (CBE-0) supplement. The proposed rule also would amend regulations to allow the RLD and ANDA holders to submit a CBE-0 labeling supplement and promptly update their product labeling to incorporate certain types of newly acquired drug safety information within the "Highlights of Prescribing Information" section for drug products with labeling in the "Physician Labeling Rule" (PLR) format. FDA contends that such actions would permit differences in labeling between the submitting RLDs and ANDA holders that would persist only for a "temporary" period of time. ASHP's comments are in response to the Agency's proposed rule published in the Federal Register on November 13, 2013.<sup>1</sup>

ASHP is the national professional organization whose 40,000 members include pharmacists, pharmacy technicians, and pharmacy students who provide patient care services in acute and ambulatory care settings, including hospitals, health systems, and clinics. For more than 70 years, the Society has been on the forefront of efforts to improve medication use and enhance patient safety.

ASHP's core mission contains publishing comprehensive drug information, including AHFS Drug Information (AHFS DI), a federally designated official compendium of professional prescribing

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<sup>1</sup> Federal Register. No. 219. Vol. 78. Pages 67985 - 67999.

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information. ASHP also publishes AHFS Consumer Medication Information, a patient drug database, which is widely accessed via the National Library of Medicine's MedlinePlus. A key element of this publishing effort has been the critical review of all aspects of professional drug labeling for almost 60 years.

Also in 1975, FDA contracted with ASHP to develop a class prescription labeling system. ASHP exhaustively applied this system to 20 major therapeutic classes and subclasses of drugs, developing standard, objective professional class labeling for safe and effective use that FDA applied to numerous individual drug products included in these classes. ASHP currently is part of a team of highly specialized life sciences subject matter experts, led by Reed Technology, who were awarded FDA's Prescription Drug Labeling Improvement and Enhancement Initiative (PDLI-EI) contract in September 2013. The purpose of this contract is to provide FDA's Center for Drug Evaluation and Research (CDER) with the necessary services to complete a number of projects planned over 5 years aimed at improving and enhancing prescription drug labeling.

ASHP also serves in key leadership positions within the National Council for Prescription Drug Programs (NCPDP) and the SPL Working Group (formed by the Pharmaceutical Research and Manufacturers Association [PhRMA] and Health Language Seven [HL7] Task Group) that are focused on advising FDA on structured product labeling (SPL) and has been actively engaged at high levels with the National Library of Medicine (NLM) and FDA concerning its DailyMed website repository of SPL.

As a result of this long and extensive experience with prescription drug labeling, ASHP is in a unique position to comment on FDA's current proposed rule. ASHP also has a long history advocating safe medication use, and as such supports expanded opportunities for updating prescription labeling promptly to reflect newly acquired drug safety data. That said, the Society is concerned that FDA can implement its proposed rule effectively, consistently, and contemporaneously to ensure that all stakeholders, including healthcare professionals, publishers, and patients, will be accessing complete, accurate, and up-to-date safety information regardless of the labeling source (RLD or any of multiple generics).

FDA has proposed several key components aimed at mitigating these concerns, such as timely ANDA advisement requirements to the RLD, web-based notification of healthcare professionals and others, and the possible penalty of ANDA approval withdrawal for failure to achieve timely labeling consistency. However, despite these proposed steps, ASHP remains concerned that the rule, if finalized, would create confusion among health care professionals, drug information publishers, and patients.

## Background

The FDA has historically faced challenges maintaining consistent and current prescription drug labels, which ultimately impact patient safety. Even under the current regulatory environment where CBE-0 supplements are limited to the RLD FDA-approved professional labels for generic drugs often are out of date, lack key safety or benefit information, and can be inconsistent or even contradictory. Such problems recently were detailed in ASHP's oral and written testimony before the Senate Special Committee on Aging concerning "Protecting Seniors from Medication Labeling Mistakes."<sup>2</sup> These deficiencies contribute importantly to ASHP's concerns about the Agency's ability to effectively implement its proposed amendment to CBE-0 supplement regulations.

As a result of expanded FDA authority in 1962 to enforce substantiation of efficacy claims, one of the first major efforts to address the problem with labeling standards came with the Drug Efficacy Study Implementation (DESI) review and resultant labeling revisions. Although started in the early 1960s, this important evaluation of safety and efficacy claims and approval of labeling that meets current standards continues even today. As a result, a considerable number of drug products have never been subjected to FDA approval employing modern standards of safety, efficacy, and labeling.<sup>3,4</sup> This "unapproved drug" status has resulted in stakeholder confusion and concern, including Federal agencies such as the Centers for Medicare & Medicaid Services.<sup>5,6</sup>

A second major effort to address the problem of labeling standards and associated deficiencies occurred with FDA's development of consistent drug-class labeling starting in the mid-1970s. A more recent example to address this problem came with the Prescription Drug Labeling Improvement and Enhancement Initiative begun in late 2013 aimed at addressing the

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<sup>2</sup> McEvoy GK. Testimony and Statement for the Record submitted by the American Society of Health-System Pharmacists. 2013 Dec 11 available at

[http://www.aging.senate.gov/imo/media/doc/McEvoy\\_12\\_11\\_13.pdf](http://www.aging.senate.gov/imo/media/doc/McEvoy_12_11_13.pdf)

<sup>3</sup> Food and Drug Administration. Unapproved Prescription Drugs: Drugs Marketed in the United States that do not have Required FDA Approval, Accessed 2014 Mar 3 at

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/default.htm>

<sup>4</sup> Food and Drug Administration. Guidance for FDA Staff and Industry: Marketed Unapproved Drugs—Compliance Policy Guide. 2011 Sep 19 available

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070290.pdf>

<sup>5</sup> Academy of Managed Care Pharmacy. Practice Advisory on Unapproved Medications. Approved by the AMCP Board 2009 Oct and available at <http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=10095>

<sup>6</sup> PR Newswire. Avalere Report Shows Unapproved Prescription Drugs Dropped from CMS Formulary Reference File. <http://www.prnewswire.com/news-releases/avalere-report-shows-unapproved-prescription-drugs-dropped-from-cms-formulary-reference-file-57254562.html>

substantial backlog of professional labeling that has not been updated since 2001 to meet FDA's current PLR labeling standard.

These labeling deficiencies have been acknowledged by CDER's Office of New Drugs in 2008 to the House Committee on Oversight and Government Reform.<sup>7</sup>

“[It is] a false assumption that the FDA approved labeling is fully accurate and up-to-date....we know that many current approved drug labels are out of date and in many cases contain incorrect information.” And “...it is unwise to suggest that FDA-approved labeling is always up-to-date and always contains a full and complete listing of all pertinent risk information.”

In 2006, FDA published its final rule that revised the content and format requirements for prescription labeling to make it easier to access, read, and use.<sup>8</sup> The rule is commonly referred to as the “physician labeling rule” (PLR). Older drugs approved before June 30, 2001 were not subject to the mandatory PLR conversion requirement, but FDA strongly encouraged all applicants to voluntarily convert the labeling of their drug products to the PLR format. However, to date only 15% of all prescription drug labels had been converted to the PLR format as of November 2012.<sup>9</sup> Generic drugs approved under an ANDA are not required to convert their labeling to PLR format unless the RLD approved in an NDA has converted to this format; only 10% of generic labels were in PLR as of November 2012. Based on estimates from DailyMed postings, that would mean that potentially thousands of prescription drug labels do not meet FDA's current PLR labeling standard. This substantial backlog of outdated labeling is perhaps the most important deficiency affecting prescription drug labeling today.

Problems with drug safety labeling inconsistencies among the RLD and associated equivalent generics also has been documented in a recent study employing natural language processing (NLP) analysis of adverse drug reactions (ADRs) in 9105 SPLs for 1540 drugs.<sup>10</sup> Almost 70% of drugs available from multiple manufacturers had discrepancies in ADR labeling despite the FDA

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<sup>7</sup> United States House of Representatives Committee on Oversight and Government Reform. Majority Staff Report: FDA Career Staff Objected to Agency Preemption Policies. 2008 Oct and available at <http://oversight-archive.waxman.house.gov/documents/20081029102934.pdf>

<sup>8</sup> Food and Drug Administration. Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products. Final Rule. Docket No. 200N-1269, RIN 0910-AA94 (21 CFR Parts 201, 314, and 601) Federal Register. 2006; 71:3922-97.

<sup>9</sup> Food and Drug Administration. Center for Drug Evaluation and Research; Prescription Drug Labeling Improvement and Enhancement Initiative; Request for Comments and Information. Docket No. FDA-2013-N-0059 (21 CFR 201, 314, and 601). Federal Register. 2013; 78:8446-8. Available at <https://www.federalregister.gov/articles/2013/02/06/2013-02528/center-for-drug-evaluation-and-research-prescription-drug-labeling-improvement-and-enhancement>

<sup>10</sup> Duke J eta I. Consistency in the Safety Labeling of Bioequivalent Medications. *Pharmacoepidemiol Drug Saf.* 2012; 22:294-301.

requirement that they agree. The authors concluded that such labeling differences may complicate practice, raising the possibility that important safety information may be missed, and that the RLDs generally contain the most comprehensive safety information. As a result, they recommended that the RLD (branded product) label be referenced for safety information even when a patient is receiving a generic. However, under FDA's current proposal to allow generic labels to be revised via a CBE-0 supplement independently of the RLD, such advice no longer would hold true. Under either the existing CBE-0 scenario or FDA's newly proposed one, this study clearly shows the challenges FDA has faced in enforcing labeling consistency, one that will be exacerbated greatly with the proposed change in CBE-0 supplement filings.

Although designed to evaluate safety information discrepancies among drugs within the same class, a recent study of black box warning labeling also showed FDA's difficulty in maintaining labeling consistency, even for the strongest medication-related safety warnings.<sup>11</sup> Other examples of labeling consistency and currency problems were included in ASHP's recent Senate testimony.<sup>12</sup>

While ASHP applauds FDA for attempting to expand the opportunities for timely inclusion of newly acquired drug safety information in professional labeling, we have considerable reservations about the confusion and potential drug safety ramifications that may result from the proposed rule. We remain concerned that the Agency would be able to ensure that the labeling for the RLD and all generic equivalents would consistently include the same newly acquired safety information initiated by a generic manufacturer's CBE-0 supplement in a timely manner.

### **Problems with Effectively Coordinating Critical Drug Safety Information**

FDA has not historically linked various safety notices about drugs directly to their corresponding labels. As a result, stakeholders must navigate a complex array of notification locations (web pages) in attempting to assemble the critical safety puzzle. Ideally, they should only need to access one location, associated with the prescription label itself posted on DailyMed, to access all relevant drug safety information for all affected products contemporaneously, whether already incorporated into the associated label or not. It is not realistic to expect that prescribers and other healthcare professionals and stakeholders would routinely navigate FDA's website(s) to locate all the safety notifications and other information that might apply to a particular drug. Therefore, in the context of today's clinical environment, simple notification alone, when not specifically and directly linked to all affected drug products and not

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<sup>11</sup> Panagiotou OA et al. Different Black Box Warning Labeling for Same-Class Drugs. *J Gen Intern Med.* 2011; 26:603-10.

<sup>12</sup> McEvoy GK. Testimony and Statement for the Record submitted by the American Society of Health-System Pharmacists.

coordinated with healthcare professional behaviors and workflow processes, is an ineffective means of ensuring FDA's goal for communicating newly acquired drug safety data in a timely fashion.

Just a few of the various portions of FDA's website that healthcare professionals and other stakeholders would need to navigate includes MedWatch notices, risk evaluation and mitigation strategy (REMS) information, safety alerts, safety labeling change summaries, early safety communications, follow-up early safety communications, information for healthcare professional sheets, public health advisories, drug safety statements, medication guides, the full labeling itself, and others. Add to this FDA's newly proposed dedicated web page (or, alternative, modification of an existing web page) on CBE-0 supplements and one can see the burdensome complexities that healthcare providers and other stakeholders face in keeping abreast of current important drug safety information.

Exacerbating this problem further is FDA's current practice of posting labeling not directly drawn from DailyMed, the intended most comprehensive up-to-date source of this information, on other portions of its website. This is particularly problematic when the Drugs portion of FDA's website directs "Healthcare Professionals" to "Drugs@FDA,"<sup>13</sup> which does not necessarily include the most up-to-date labeling version, rather than to "DailyMed."

Because there currently is a confusing array of drug product labeling available on various sites on the Internet, including manufacturer-hosted sites and several government sites, it is critical that a single reliable and trusted source of the most current information be available for access by healthcare professionals, consumers, and importantly the downstream users of these data. DailyMed was created by FDA and the National Library of Medicine (NLM) to serve this purpose. However, it is not always clear to those seeking such data that these other sources may not include the most current information.

Therefore, it is critically important that FDA address the communication shortcomings of the current approach to drug safety information dissemination before implementing their proposed changes in CBE-0 supplements. Otherwise, the Agency cannot ensure that this critical newly acquired safety information will get into the hands of prescribers and others involved in drug therapy decisions and safety monitoring in a timely and predictable fashion.

Through its leadership in various NCPDP-sponsored and other initiatives, ASHP has served a key role in advocating such changes (e.g., SPL as a source of REMS information, use of DailyMed as a centralized source of all drug product information) and is available to help FDA address concerns about effective coordinated drug safety communication.

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<sup>13</sup> <http://www.fda.gov/Drugs/ResourcesForYou/HealthProfessionals/default.htm>

### **CBE-0 Supplements to Highlights Section of PLR**

ASHP applauds FDA in proposing to correct a current limitation in CBE-0 submissions by eliminating the requirement for the Agency's preapproval on any proposed changes to the "Highlights of Prescribing Information" section of PLR labeling. This limitation is a controversial artifact of the Preamble to the Agency's 2006 revised Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, and unnecessarily limited a manufacturer's ability to make timely changes to this important section of the labeling without prior FDA review and approval. In balance, the importance of being able to revise the Highlights section in a timely manner for newly acquired drug safety information outweighs the concerns.

### **Key Issues with Amended CBE-0 Supplement Regulations for ANDA Holders**

Because of the concerns discussed above with the FDA's approach to ensuring consistent and up-to-date professional drug labeling for equivalent drug products, ASHP is concerned the proposed rule would result in healthcare professionals, drug information publishers, and patients accessing incomplete or outdated information. Even under the current scenario where CBE-0 labeling supplements for newly acquired critical safety information is limited to the RLD, the labels for equivalent generic products are often not the same. For these reasons, ASHP remains concerned that current limitations with the FDA's label revision process will only be compounded when generic manufacturers could independently initiate a CBE-0 safety supplement as proposed. It is difficult to envision how the Agency could be successful with this far more complex scenario without substantial institutional changes in how it manages labeling changes and drug safety communication.

Adding to our concern is that, under current regulations, generic manufacturers only have limited access to the full context of safety information about their drugs. Thus, FDA will need to assume a key role in reviewing all the accumulated data available and determining the tone of proposed labeling revisions as it conducts its review and approval of final labeling for each CBE-0 supplement.

In summary, ASHP's concerns focus on the following:

- The history of challenges that the FDA has experienced in maintaining consistency and timeliness of professional prescribing information
- Concern with FDA's ability to effectively manage and coordinate its proposed CBE-0 changes and ensure enforcement of the 30-day ANDA advisement requirement by the

RLD and all other ANDA holders. Multiple and uncoordinated sources of current drug safety and prescribing data

- Implementation of proposed revisions in CBE-0 supplements unless corresponding institutional changes in labeling procedures and communication are developed and effectively implemented

ASHP, as part of its mission, supports the safe and effective use of medications. Increasing the timely communication of newly acquired drug safety information is a laudable goal of FDA's current proposal concerning CBE-0 supplements. However, the Agency's current proposal does not include sufficient safeguards to ensure that all stakeholders—prescribers and other healthcare professionals, drug information and knowledgebase publishers, and patients—will be ensured timely consistent access to this information regardless of the manufacturer (RLD or any of the multiple generic manufacturers). Therefore, as described in this letter, ASHP recommends that FDA take steps to ensure the following prior to implementation of its proposed changes:

- Change the Agency's current methods for drug safety communication into a coordinated single-access point through DailyMed.
  - Various web pages of distinct types of drug safety information can be maintained as source action-type summaries (which would continue to serve different change monitoring purposes),
  - All key safety information should be linked to each affected drug label posted on DailyMed.
- Increase the Agency's efforts at ensuring drug label consistency, including heightened enforcement of existing and newly proposed authority, so that stakeholders can be assured they are accessing the most current and complete information regardless of labeling source
- Serve a key role during final approval of all proposed CBE-0 supplements to address the limited access that generic manufacturers have to the full array of drug safety data and provide needed context concerning the merits and tone of proposed labeling changes



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The Society appreciates the opportunity to provide ASHP's perspective on proposed revisions to CBE-0 supplement regulations. Please contact me if you have any questions or wish to discuss our comments further. I can be reached by telephone at 301-664-8806, or by e-mail at [ctopoleski@ashp.org](mailto:ctopoleski@ashp.org).

Sincerely,

Christopher J. Topoleski  
Director, Federal Regulatory Affairs