



California State Board of Pharmacy

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BUSINESS, CONSUMER SERVICES AND HOUSING AGENCY

DEPARTMENT OF CONSUMER AFFAIRS

GOVERNOR EDMUND G. BROWN JR.

Communication and Public Education Committee
Meeting Materials for the April 1, 2014 Meeting

Members

Ryan Brooks, Chair, Public Member

Albert Wong, PharmD, Professional Member

Lavonza Butler, Professional Member

Ramon Castellblanch, PhD, Public Member

Shirley Wheat, Public Member

1. FOR INFORMATION: Presentation by Mpack Systems on New Product Design for Pharmacy Prescription Containers

Attachment 1

Mpack Systems will present information on its new design for pharmacy prescription packaging. Presenting will be Bill Negrini, president; Bill Hartig, RPh, president of PreScripts and consulting pharmacist; Richard Lee, vice president; all from Mpack Systems.

Materials for this presentation are provided as **Attachment 1**.

2. FOR DISCUSSION AND POSSIBLE ACTION: Resumption of the Committee's Assessment of California's Patient-Centered Labeling Requirements

Attachment 2

Background:

Title 16 California Code of Regulations section 1707.5 specifies requirements for patient-centered labels for prescription drug containers. When the board promulgated these requirements, there was much public comment from numerous stakeholders. As such, the board included in subdivision (e) a requirement that the board re-evaluate the requirements by December 2013 to ensure optimal conformance with Business and Professions Code Section 4076.5, which directed the board to promulgate regulations for improved prescription container label design that would be patient-centered.

The committee began a review of the regulations in April 2013. Discussion materials are provided in **Attachment 2**.

At the October 2013 Board Meeting, the board reviewed and discussed some of the committee's recommendations, but lacked sufficient time to finish the discussion. The board directed the matter back to this committee for additional discussion and refinement. The portion of the minutes from the October 2013 Board Meeting that cover patient centered labeling is provided in **Attachment 2**.

Nevertheless, at the October Board Meeting, the board voted to amend two items of 1707.5(a) – requiring 12 point font for all elements of the patient centered label, and an express prohibition that nothing but the designated patient-centered elements appear in the 50 percent of the label space dedicated to the patient-centered labels. At the January 2014 Board Meeting, these two changes were moved to notice for public comment to initiate a rulemaking, and are not a part of the discussion scheduled for this committee meeting. This proposed language is:

1707.5.(a)(1) Each of the following items, and only these four items, shall be clustered into one area of the label that comprises at least 50 percent of the label. Each item shall be printed in ~~at least a 10-point sans serif typeface or, if requested by the consumer,~~ at least a 12-point **sans serif** typeface, and listed in the following order:

- A. Name of the patient
- B. Name of the drug and strength of the drug. For the purposes of this section, name of the drug” means either the manufacturer’s trade name of the drug, or the generic name and the name of the manufacturer.
- C. The directions for use
- D. The condition or purpose, if it is indicated on the prescription.

At this meeting:

The committee has been tasked by the board to discuss the following items and other elements relating to patient-centered labels, and bring recommendations back to the board. To aid the committee in its discussion, each item will be addressed individually.

a. Should Section 1707.5(a)(1)(B) Require Listing of the Manufacturer’s Name in the Patient-Centered Clustered Area of the Label When a Generic Drug Is Dispensed?

Current statutory law for prescription container labels requires that if a generic drug is dispensed, then the manufacturer’s name must also appear somewhere on the label. If a brand name is dispensed, then no manufacturer’s name is required on the label.

In a prior meeting, the committee had recommended to the board the removal from 1707.5 (a)(1)(B) of “and the name of the manufacturer” when a generic is dispensed.

At the October Board Meeting, it was pointed out that the manufacturer name is still required by Business and Professions Code section 4076 to appear elsewhere

on the label every time a generic is dispensed. There was disagreement as to whether the manufacturer name needed to be in the patient-centered section.

At this meeting:

Language to remove the manufacturer's name from the patient-centered area (but it would still be required to appear elsewhere on the label) is provided below:

- (a) Labels on drug containers dispensed to patients in California shall conform to the following format:
 - (1) Each of the following items shall be clustered into one area of the label that comprises at least 50 percent of the label. Each item shall be printed in at least a 10-point sans serif typeface or, if requested by the consumer, at least a 12-point typeface, and listed in the following order:
 - (A) Name of the patient
 - (B) Name of the drug and strength of the drug. For the purposes of this section, "name of the drug" means either the manufacturer's trade name of the drug, or the generic name ~~and the name of the manufacturer.~~

b. Should Changes Be Made to 1707.5(a)(1)(B) regarding the Name of the Drug and Strength of the Drug to Improve Patient Understanding of the Medication?

This agenda item seems to duplicate the discussion that will occur in agenda items (a) and (c), so it is being dropped as needing to be discussed here.

c. When a Generic Drug Is Dispensed, Should the Generic Equivalent Drug Dispensed to a Patient Be Referenced Back to the Brand Name, e.g., Phrased as "Generic for (brand name)_____"?

Attachment 2c

At the January Committee Meeting, the committee discussed this item and sought information on how other states handle this situation. Arizona has regulations in this area. See **Attachment 2c**.

The regulations for Arizona state that when a physician writes for a brand name and the pharmacist fills with a generic then both names must appear on the label. If the doctor writes for a generic, then only the generic name appears on the label.

At the last committee meeting there was some interest in including the brand name and "generic for _____" in the patient-centered portion of the label. A question was raised as to how long to continue to do such labeling once the brand name patent has expired.

One solution could be to include “generic for _____” and include the brand name, and to require the brand name be listed for a period of time (e.g., five years after patent’s expiration), or leave up to the professional judgment of the pharmacist. Language to do this is provided below:

- (1) Each of the following items shall be clustered into one area of the label that comprises at least 50 percent of the label. Each item shall be printed in at least a 10-point sans serif typeface or, if requested by the consumer, at least a 12-point typeface, and listed in the following order:
 - (A) Name of the patient
 - (B) Name of the drug and strength of the drug. For the purposes of this section, “name of the drug” means either the manufacturer’s trade name of the drug, or the generic name and the statement “generic for _____” where the brand name is inserted into the parentheses. If it has been at least five years since the expiration of the brand name’s patent or if in the professional judgment of the pharmacist the brand name is no longer widely used, the label may list only the generic name of the drug and the name of the manufacturer.

d. Should Purpose or Condition Be a General Requirement for Labels?

Existing regulation section 1707.5(a)(1)(D) states that purpose is to be included on the patient-centered portion of the label if it is indicated on the prescription, which is consistent with the statutory requirements.

The board has discussed multiple times, including both during promulgation of the regulation and as part of evaluation of the patient-centered labels, possible regulation or statutory requirements to more frequently ensure purpose appears on the label. The options for how to make an addition, and whether purpose on a label could be considered a violation of HIPAA, was directed to Board Counsel Michael Santiago to research at the last committee meeting.

Existing regulation section 1707.5(a)(1)(D) states that purpose is to be included on the patient-centered portion of the label if it is indicated on the prescription, which is consistent with the statutory requirements in the Business and Professions Code.

During committee discussions in January, it was stated that if purpose is not indicated, a pharmacist may use professional judgment to determine the purpose or may contact the prescriber. The Medical Board of California generally has been supportive of including purpose on prescription labels and research has indicated that patients also want purpose on the label. It was also pointed out that the California Senior Legislature may pursue legislation on this because they want purpose on the label. We are unaware of the introduction of such legislation thus far in 2014.

There is generally strong support from the NABP, USP and researchers who have developed guidelines for patient-centered regulations to support purpose being on the label.

e. Should the Existing Requirements for “Added Emphasis” in the Patient-Centered Area of the Prescription Label Be Modified?

At the January committee meeting, there was no committee or public discussion on this item. It is repeated here just to ensure the committee has no interest in modifications to this element.

f. Translated Directions for Use Are Available on the Board’s Website. Should the Board Require Use of Them to Aid Patients with Limited English Proficiency?

Attachment 2f

The committee and the board have previously discussed the requirement to use translations on the labels. At this point in the meeting the committee will have the opportunity to resume this discussion.

Attachment 2f contains the translations from the board website in Spanish and Chinese. It also contains an op-ed written by a physician about translations on prescription bottles.

g. Should the Board Consider Technology Standards to Enhance the Patient-Centered Requirements?

At the last committee meeting, Ms. Herold commented that many some pharmacies are able to provide pictures of the pill on the prescription label, instead of the verbal description of the medication -- which is a statutory requirement for all labels. She asked the committee if they were interested in discussing any technology standards or requiring items like a picture of the pill on the label to replace the description. Mr. Brooks and Dr. Castellblanch requested data on the type of technology available in community pharmacies before making additional requirements in this area.

Staff has not yet identified the degree to which pharmacies have the existing capacity to use more advanced technology standards.

3. **FOR INFORMATION: Availability of Options for Prescription Labels for Visually Impaired Patients**

Attachment 3

The board was recently made aware of a new technology to aid visually impaired patients in taking their medications. **Attachment 3** contains this information.

4. **FOR INFORMATION: Proposal by the Federal Food and Drug Administration on “Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products”**

Attachment 4

As stated in the summary of the proposed rule change (**Attachment 4**), the Food and Drug Administration late last year proposed to amend its regulations to revise procedures for generic drug manufacturers who hold a generic drug approval to change the product labeling to reflect certain types of newly acquired information in advance of the FDA's actual review of the change. The proposed rule would permit generic drug manufacturers who are approved to manufacture a generic version of a brand-name drug to distribute revised product labeling that differs in certain respects, on a temporary basis, from the labeling of its reference listed drug previously submitted to the FDA.

The proposed rule describes the process by which information regarding labeling changes would be made publicly available during FDA's review of the labeling change, and clarifies requirements for all ANDA holders (generic manufacturers) to submit conforming labeling revisions after FDA has taken an action on the brand name or generic's manufacturer's labeling supplement.

The proposed rule would enable generic manufacturers to update product labeling promptly to reflect certain types of newly acquired information related to drug safety, essentially if information about the brand name counterpart becomes available. The GPhA, which represents the generic industry, does not support this proposal, and said that any negative effects associated with a brand name drug should be on the label of the brand name product, not to the generic version their members manufacture.

The board took no action to submit comments on this requirement, nor did it review the proposal.

This is provided for information in the event the board wishes to make a statement regarding this proposed requirement.

Attachment 4 contains the FDA proposal from The Federal Register. It also contains an L.A Times article on the subject.

5. **FOR INFORMATION: The National Association of Boards of Pharmacy’s Launch of “.pharmacy” to Identify Legitimate Internet Web Sites for Prescription Drugs**

Attachment 5

The National Association of Boards of Pharmacy recently received approval from the ICANN Board (which approves the use of top level domains -- e.g., controlling those who can use suffixes such as “.com,” “.org” or other addresses for web sites) to approve those who can use the “.pharmacy” domain. This will enable the NABP to establish who can use .pharmacy as a suffix, thereby enabling them to approve “legitimate” Internet businesses (those who comply with the NABP’s standards). Currently 97 percent of the drug outlets operating drug selling websites are illegitimate according to the NABP.

Attachment 5 contains the recent report on “.pharmacy” by the National Association of Boards of Pharmacy.

6. **FOR INFORMATION: Update on *The Script***

The Script is scheduled to go into design next week. This edition focuses on new laws for 2014 and disciplinary actions. We intend to resume at least biannual production of this newsletter from this point forward.

7. **FOR INFORMATION: Review of the Board’s Public Service Announcement and Video Developed on Prescription Drug Abuse**

Attachment 6

Public service announcements on prescription drug abuse have been developed for both radio and television to inform the public about the prescription drug abuse epidemic and give simple steps that can be taken in the home to keep prescription medications out of the hands of teens. There was a print format of these available, and very recently, now a video format of the PSAs produced. The committee will be able to view the videos during this meeting.

Attachment 6 contains the three written public service announcements.

8. **FOR INFORMATION: Update on the Board’s Consumer Education Materials on Counterfeit Drugs and a Newsletter Article for the Medical Board’s Newsletter**

Attachment 7

A new online brochure on counterfeit drugs is in the design phase and is expected to be completed in April.

Staff also developed an article on patient centered prescription labels was written to appear in the upcoming Medical Board newsletter.

Attachment 7 contains the article on patient centered labels for the Medical Board newsletter.

9. FOR INFORMATION: Update on Media Activity

Attachment 8

Attachment 8 containing recent media contacts handled by the office will be distributed at the meeting.

10. FOR INFORMATION: Public Continuing Education Training Session by the California State Board of Pharmacy and Federal Drug Enforcement Administration Held January 31, 2014, in Sacramento

This item is included in the list in item 11 below.

11. FOR INFORMATION: Public Outreach Activities Conducted by the Board

Since mid-January, board staff has joined with the DEA to host two six-hour CE sessions for pharmacists on prescription drug abuse and a pharmacist's corresponding responsibility.

- Public Continuing Education Training Session Provided by the California State Board of Pharmacy, the Los Angeles Field Division of the Drug Enforcement Administration and County of Orange Health Care Agency: January 22, 2014 in Brea, CA

This continuing education program for pharmacists was held in conjunction with a new partner, the County of Orange Health Care Agency. Nearly 200 individuals attended this training.

- State Board of Pharmacy and Federal Drug Enforcement Administration Held January 31, 2014 in Sacramento

This six-hour CE presentation featured Federal DEA Diversion Program Manager Joseph Rannazzisi and again the board's strengthened corresponding responsibility component. It was the first time this presentation was provided in Sacramento.

Other Public Outreach:

- January 24: Executive Officer Herold provides an update on Board of Pharmacy activities to the CSHP Board at a meeting in Sacramento
- February 7: Executive Officer Herold provides an update on Board of Pharmacy activities at the quarterly meeting of the Medical Board of California in San Francisco
- February 27: Executive Officer Herold provides a presentation on pharmaceutical supply chain problems that violate the law to a national meeting of supply chain compliance managers in San Diego
- March 4: Executive Officer Herold provides a presentation on the Board of Pharmacy and enforcement activities to students at Touro University
- March 5: Executive Officer Herold provides a presentation on implementation of new pharmacy law at CSHP's and CPhA's Legislative Day
- March 19: Executive Officer Herold provides a presentation on the board's position on biosimilars via a webinar connection to a conference held in Philadelphia
- March 20 and 21: Executive Officer Herold attends the FDA's 50-State Conference on Drug Compounding in Washington DC. She provides a presentation on California's Sterile Compounding experiences
- March 26: Executive Officer Herold provides a presentation to the Senate Environmental Health Committee on drug take back programs and drug diversion in pharmacies

12. Public Comment for Items Not on the Agenda, Matters for Future Meetings*

**(Note: the committee may not discuss or take action on any matter raised during the public comment section that is not included on this agenda, except to decide to place the matter on the agenda of a future meeting. Government Code Sections 11125 and 11125.7(a))*

Adjournment

3 p.m.

Attachment 1



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Viials • Compliance Tools • Pharmacy Automation

March 27, 2014

Subject: Mpack Compliance to the Patient Protection and Affordable Care Act

Dear Ms. Emard,

The enactment of the 2010 Patient Protection and Affordable Care Act (“Obamacare”, or ACA) brings a new focus on quality improvement, including incentives for high quality health plans. CMS has initiated substantial quality bonus payments (QBPs) for health insurance companies that administer Medicare Advantage plans based on their Medicare star rating. The Medicare star ratings include PQA quality measures of medication adherence, as well as measures of medication use safety. PQA measures account for 48% of a health plan’s Medicare Part D star rating. QBP-based Medicare rebates are awarded to plans achieving a three-star rating or higher according to a sliding scale based on star performance. This has created a new focus on medication adherence by health plans.

To capitalize on this new shift in the marketplace, health plans are utilizing a variety of methods to try and improve patient performance on adherence metrics. Formularies, clinical strategies, network contracts, marketing/promotions are all being aligned with star measures strategies. Health plans will be increasingly leveraging their network pharmacies, such that for some plans network pharmacies are judged according to their performance on PQA adherence and safety measures. There are several health plans and PBMs developing pay-for-performance bonus structures, in which network pharmacies with strong performances on PQA measures are given additional payments from the health plan or PBM. One such health plan you are likely very aware of: the Inland Empire Health Plan based in San Bernardino, which launched its P4P bonus program in October of 2013. Pharmacies are responding by utilizing new methods of addressing medication adherence.

All of the above cannot produce quality results unless the starting point is a fully compliant packaged product and system. Products packaged under GMP are more than 20% safer by reducing mistakes made after the product hits the pharmacy receiving dock. Many mistakes are made tracking and tracing drugs after the product leaves the distribution centers or manufacturer and is received by the retail pharmacy. The pour and count system and will call are the largest areas of human intervention and thus pose the largest risk for errors.



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Let's review the high-level situation:

- 4.3 billion prescriptions per year
- 82% are for the Top 100 drugs, many with similar and easily-confused names
- That's 3.5 billion scripts per year

If medication identification processes produce only 1 error per 1,000 transactions (99.99%), that equals 3.5 million mistakes per year, many with potentially fatal results!

Medication adherence is fast becoming a required core competency for pharmacists, and they need to be aware of the tools that are available to support medication adherence, including the m-pack container. The m-pack is not a panacea - no adherence intervention is. But it is part of the solution. We have preliminary data, which has not been submitted for peer review, and is admittedly from a biased source, namely us, but nonetheless it is clear:

- Significant elevation in medication adherence associated with our m-pack containers due to the 80% increase in label space providing patient information in large, clear, and easily-read type, with more detailed instructions
- Reduced incidence of cross-contamination from other medications because we have eliminated the pour, count and fill process at the pharmacy by using GMP pre-packaged medications
- Our 5mRx dispensing system eliminates the need for a will call system and the associated risks. With that the need for "put back to stock" items that were not picked up is also eliminated. An estimated 20-25% of filled scripts are not picked up.
- Lower incidence of medication dispensing errors resulting from mislabeling or providing the wrong drug to the patient. The 5mRx software does not allow for the incorrect drug to be dispensed.
- Distinct patient preference for the m-pack container over traditional round vials – easier to open, easier to dispense single tablets, spill-resistant, and CR features



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- Safer delivery of medications through the mail without damage to the package
- QR coded labels that link directly to a pharmacist giving clear instructions on how to take the medication, potential side effects, and related information
- The opportunity to set up text messages to remind you to take your medication on time with the ability to confirm that you have taken your medication when texted.

The m-pack container and 5mRx facilitates the quality improvement objectives outlined above, with clear and dramatic advantages over round vials, blister cards, slide boxes, and other containers.

In addition the federal government passed a HR 3204, The New Drug Safety and Security Act which mandates significant changes in the requirements for pharmacies and wholesalers to manage the supply stream of prescription drugs. Included but limited to a requirement for pedigree to patient level and serialization of packaging to be included in the pedigree. These changes must be adhered to with 4 years; however, all of the MPS and 5mRx offerings comply with this new mandate today. We have proven that it is possible to stay ahead of and lead constructive change in the pharmacy industry at a time when many companies are standing by waiting for mandates. The goals of the medication supply chain should revolve around patient safety and compliance while enhancing supply chain efficiencies and performance.

We ask just one question: how can we help others implement constructive change?

Sincerely,

A handwritten signature in blue ink, appearing to read 'William Negrini', with a long horizontal flourish extending to the right.

William Negrini
President – Mpack Systems and 5mRx
419-481-0186

Attachment 2

April 2013 Committee Discussion

by 17 inches and can be ordered from the Board. The translated posters can also be downloaded from the Board's website under the "Publications" tab and printed on 8.5 inch x 11 inch or 11 inch by 17 inch paper.

- b. The video display format of the Notice to Consumers is available in English or Spanish for pharmacies that request it. The video is also available for download from the Board's website under the "Publications" tab. This is explained in the Board's mailing.
- c. The Notice of Interpreter Availability poster will also be included in the Notice to Consumers mailing. The poster is 8.5 inches by 11 inches and will be available for download from the Board's website.

A letter from Executive Officer Herold explaining the regulations for placement and display of the posters was included with the mailing.

The regulations also provide provisions for pharmacies to develop their own video version of the Notice to Consumers poster and the Notice of Interpreter Availability. At the February Board meeting, the Board directed that these exemption requests be sent to this committee for action.

There were no comments from the committee or the public.

3. Discussion of Guidelines for Prescription Container Labels developed by the United States Pharmacopeia

Mr. Brooks referenced The United States Pharmacopeia's (USP) recommendations for prescription container labels provided in the meeting materials.

The Board's regulations for patient-centered prescription container labels (16 California Code of Regulations section 1707.5) contain a provision committing the Board to review the Board's regulation requirements by December 2013. The committee initiated the review of this regulation during the April meeting by discussing the following elements:

a. United States Pharmacopeia Guidelines for Prescription Drug Labels

The United States Pharmacopeia recently released their recommendations for prescription container labels. Review of the material in USP's guidelines would be one source of information useful for comparison of the Board's regulations with guidelines for premium presentation and focus on patient needs.

It is important to note that USP's recommendations already closely resemble the Board's existing regulation requirements for patient-centered prescription container labels, specifically:

- Organize the prescription label in a patient-centered way. Feature the information patients most often seek out or need to understand about taking the medication safely.
 - Emphasize: directions
 - At the top of the label place: patient's name

- Drug name (spell out full brand AND generic name)
 - Strength
 - Explicit and clear directions for use in simple language
- Prescription directions should follow a standard format so the patient can expect where to find information.
- Less critical information can be placed elsewhere and in a matter where it will not “supersede” critical patient information, and away from where it can be confused with dosing instructions
- Use language that it is clear, simplified, concise and familiar, and in a standardized manner. Use common terms and full sentences. Do not use unfamiliar words, Latin terms or medical jargon
- Use simplified, standardized sentences that have been developed to ensure ease understanding the directions (by seeking comment from diverse consumers)
- Separate dose from the timing of each dose to clearly explain how many pills to take and specify if there is an appropriate time to take them (morning, noon, evening, bedtime).
- Do not use alphabetic characters for numbers (not in CA’s)
- Use standardized directions whenever possible.
- Avoid ambiguous terms such as “take as directed” (not in CA’s) unless clear and unambiguous supplemental instructions and counseling are provided
- Include purpose on the label unless patient does not want it, and if used, use “purpose for use” language such as for blood pressure rather than hypertension.
- Limit auxiliary information, and only if evidence based. (not in CA’s)
- Use icons only if vetted with the general public (not in CA’s)
- Address limited English proficiency.
- Labels should be designed so they are easy to read. Optimize typography by using:
 - High contrast print (black print on white background)
 - Large font sizes in simple, uncondensed fonts in at least 11 point if Arial, or 12 point if Times New Roman)
 - Optimize use of white space between lines (25-30 percent of font size)
 - Horizontal placement of lettering only
 - Sentence case
 - Highlighting, bolding and other typographical cues should enhance patient-centered information, but limit the number of colors used for highlighting
- Address visual impairment (not in CA’s)

Regarding addressing limited English speaking/reading patients, USP encourages directions for use in the patient’s language as well as in English. Translations should be developed using high quality translation processes (CA’s translated directions would fit this criterion).

There were no public comments.

4. Results of surveys regarding prescription container labels

a. Discussion of consumer surveys regarding prescription container labels

Chair Brooks referenced the consumer surveys soliciting feedback regarding consumer satisfaction with prescription drug container labels. An electronic version

of the survey was sent to several consumer groups including AARP, Consumers Union, and California Pan Ethnic Health Network (CPEHN), who in turn distributed it to their ListServe contacts. The survey was also translated into Chinese and Spanish by the board and distributed by CPEHN to the appropriate audiences.

Surveys were also distributed and collected in person at local Senior Scam Stopper seminars (public protection fairs) sponsored by the Contractors State License Board.

The board received a total of 1204 completed surveys. The results were referenced in the meeting materials.

b. Discussion on prescription labels in use in California pharmacies.

Chair Brooks provided that for about seven months in 2012, board inspectors collected information about what patient-centered labels were in use in California pharmacies. The results of 767 pharmacy visits are summarized in an attachment to the meeting materials.

In general, nearly 70 percent of the labels in use as found by the board's inspectors are printed in 12-point font, 15 percent use both 10 and 12 point font on the labels, and about 15 percent are printed in 10 point .

Other Material Reviewed: Availability of Audible Prescription Labeling System

The committee was provided with information about an audible prescription labeling system. A brochure describing this device was provided in the committee's meeting materials as background to the committee to some of the devices that are in use. There was no discussion during the meeting on this device.

Ms. Wheat offered that pharmacies that had a foreign-speaking staff member available were not in compliance with regulations, and that those pharmacies would actually need staff available that could speak all 12 languages. She provided that there are translation services that provide telephone translations for a small fee, and those pharmacies that were not in compliance would be cited.

Dr. Castellblanch provided that the results from the Chinese-speaking audience were very positive but that the font-size continued to be an issue for some.

Public Comment

Steve Gray, representing the California Society of Health System Pharmacists (CSHSP) and Kaiser Permanente, provided that he received feedback that many pharmacies believed an interpreter service would be expensive. Mr. Gray offered that CSHSP offers the service at no cost. He also offered that many providers offer a menu of services so the subscriber can decide which level of service they need. Typically they offer services for a flat rate, by the hour, by the month, etc. Pharmacists can contact CSHSP for more information.

Mr. Gray continued that the Board should consider inspecting labels that are being mailed into California, since they should be compliant with California regulations.

Assistant Executive Officer Anne Sodergren explained that all applicants for a non-resident pharmacy license are required to submit samples of their prescription container labels. If they do not, they are cited for a deficiency.

Mr. Gray also explained that there are machines that produce labels and in these cases the prescription is dispensed by the physician and the pharmacy is bypassed. He suggests the Medical Board be contacted with regard to this issue so the machines can be programmed to be compliant with Board regulations.

Sarah Hickey, representing the California Pan Ethnic Health Network (CPEHN) thanked the Board for their work on patient-centered labels. She inquired about the possibility of providing software on the Board website that would allow compliant labels to be printed. Dr. Castellblanch provided that private industry may develop such software in the future.

5. For Information: Evaluate patient-centered labels by December 2013 as required by California Code of Regulations Section 1707.5(e)

During the April committee meeting and over the remaining meetings of the committee this year, the committee will work on the assessment of the patient-centered regulation requirements. Information developed by the committee will be referred to the board for action or comment at the next board meeting.

Materials also provided to the committee for review of the labels were:

- The first board report to the Legislature on the efforts to implement patient-centered labeling requirements;
- Samples of patient-centered labels.

For reference: Regulation Section 1707.5

1707.5. Patient-Centered Labels for Prescription Drug Containers; Requirements

(a) Labels on drug containers dispensed to patients in California shall conform to the following format:

(1) Each of the following items shall be clustered into one area of the label that comprises at least 50 percent of the label. Each item shall be printed in at least a 10-point sans serif typeface or, if requested by the consumer, at least a 12-point typeface, and listed in the following order:

(A) Name of the patient

(B) Name of the drug and strength of the drug. For the purposes of this section, "name of the drug" means either the manufacturer's trade name of the drug, or the generic name and the name of the manufacturer.

(C) The directions for the use of the drug.

(D) The condition or purpose for which the drug was prescribed if the condition or purpose is indicated on the prescription.

(2) For added emphasis, the label shall also highlight in bold typeface or color, or use blank space to set off the items listed in subdivision (a)(1).

(3) The remaining required elements for the label specified in section 4076 of the Business and Professions Code, as well as any other items of information appearing on the label or the container shall be printed so as not to interfere with the legibility or

emphasis of the primary elements specified in paragraph (1) of subdivision (a). These additional elements may appear in any style, font, and size typeface.

(4) When applicable, directions for use shall use one of the following phrases:

- (A) Take 1 [insert appropriate dosage form] at bedtime
- (B) Take 2 [insert appropriate dosage form] at bedtime
- (C) Take 3 [insert appropriate dosage form] at bedtime
- (D) Take 1 [insert appropriate dosage form] in the morning
- (E) Take 2 [insert appropriate dosage form] in the morning
- (F) Take 3 [insert appropriate dosage form] in the morning
- (G) Take 1 [insert appropriate dosage form] in the morning, and Take 1 [insert appropriate dosage form] at bedtime
- (H) Take 2 [insert appropriate dosage form] in the morning, and Take 2 [insert appropriate dosage form] at bedtime
- (I) Take 3 [insert appropriate dosage form] in the morning, and Take 3 [insert appropriate dosage form] at bedtime
- (J) Take 1 [insert appropriate dosage form] in the morning, 1 [insert appropriate dosage form] at noon, and 1 [insert appropriate dosage form] in the evening
- (K) Take 2 [insert appropriate dosage form] in the morning, 2 [insert appropriate dosage form] at noon, and 2 [insert appropriate dosage form] in the evening
- (L) Take 3 [insert appropriate dosage form] in the morning, 3 insert appropriate dosage form] at noon, and 3 [insert appropriate dosage form] in the evening
- (M) Take 1 [insert appropriate dosage form] in the morning, 1 [insert appropriate dosage form] at noon, 1 [insert appropriate dosage form] in the evening, and 1 [insert appropriate dosage form] at bedtime
- (N) Take 2 [insert appropriate dosage form] in the morning, 2 [insert appropriate dosage form] at noon, 2 [insert appropriate dosage form] in the evening, and 2 [insert appropriate dosage form] at bedtime
- (O) Take 3 [insert appropriate dosage form] in the morning, 3 [insert appropriate dosage form] at noon, 3 [insert appropriate dosage form] in the evening, and 3 [insert appropriate dosage form] at bedtime
- (P) If you have pain, take ___ [insert appropriate dosage form] at a time. Wait at least ___ hours before taking again. Do not take more than ___ [appropriate dosage form] in one day

(b) By October 2011, and updated as necessary, the board shall publish on its Web site translation of the directions for use listed in subdivision (a)(4) into at least five languages other than English, to facilitate the use thereof by California pharmacies.

(d) The pharmacy shall have policies and procedures in place to help patients with limited or no English proficiency understand the information on the label as specified in subdivision (a) in the patient's language. The pharmacy's policies and procedures shall be specified in writing and shall include, at minimum, the selected means to identify the patient's language and to provide interpretive services in the patient's language. If interpretive services in such language are available, during all hours that the pharmacy is open, either in person by pharmacy staff or by use of a third-party interpretive service available by telephone at or adjacent to the pharmacy counter.

(e) The board shall re-evaluate the requirements of this section by December 2013 to ensure optimal conformance with Business and Professions Code section 4076.5.

(f) As used in this section, "appropriate dosage form" includes pill, caplet, capsule or tablet.

October 2013 Board Meeting Discussion

Dr. Castellblanch provided that the Legislation Committee had considered SB 204 during their committee meeting, which was drafted to require that labels be printed in 12-point font. The committee felt it was poorly drafted and voted against it.

Motion: Support a regulation to require 12 pt. font on the four major elements on a label.

M / S: Castellblanch / Brooks

S: 7 O: 0 A: 0

Committee member Veale sought clarification and suggested that current label regulations be fully accessed and vetted before a motion is made to introduce a new label regulation.

Ms. Herold provided that an alternative would be to gather all pertinent information and present Board standards to produce an informational document which would include all of the issues, questions, public hearings and deliberations necessary to fully vet the issue before moving to introduce a new regulation.

Motion: Dr. Castellblanch moved to withdraw his motion.

Chair Brooks suggested that the discussion be moved to the next Board meeting and that a special committee meeting be convened to address the current patient-centered labels.

Motion: Chair Brooks motioned that a special committee meeting be convened to address patient-centered labels and that the matter be moved to the next full Board meeting.

M / S: Brooks / Hackworth

S: 7 O: 0 A: 0

6. Discussion on Research Advisory Panel's Annual Report 2012

Chair Brooks referenced the Research Advisory Panel's Annual Report for 2012 in the meeting materials.

Pursuant to Health & Safety Code Sections 11480 & 11481, California Law requires proposed research projects involving certain opioid, stimulant, and hallucinogenic drugs classified as Schedule I and Schedule II Controlled Substances to be reviewed and authorized by the Research Advisory Panel of California in the Attorney General's Office.

The Research Advisory Panel primarily seeks to ensure the safety and protection of participating human research subjects and adequate security of the controlled substances used in the study. The panel members evaluate the scientific validity of each proposed project, and may reject proposals where the research is poorly conceived, would produce conclusions of little scientific value, or would not justify the exposure of California subjects to the risk of research.

EXCERPT OF THE MINUTES FROM THE OCTOBER 2013 BOARD MEETING

XVI. COMMUNICATION AND PUBLIC EDUCATION COMMITTEE REPORT

In Chairperson Brooks' absence, President Weisser provided a report on the Communication and Public Education Committee meeting that was held on October 7, 2013

1. Report of the Communication and Public Education Committee Meeting Held October 7, 2013

a. Review and Discussion of the 42nd Annual Report of the Research Advisory Panel of California

President Weisser reported that Patrick R. Finley, Pharm.D., is the board's appointment to the seven member advisory panel. Mr. Weisser referenced the copy of the 42nd Annual Report of the Research Advisory Panel of California (July, 2012) provided with the meeting materials. The committee recommended that Dr. Finley come to a future meeting of the committee or board to tell them more about the Advisory Panel's activities and to share additional information on studies that may be of interest to the board or related to the pharmacy profession.

Discussion

There were no comments from the board or from the public

b. Discussion on Requests from California Pharmacies for Exemption from Title 16 California Code of Regulations Section 1707.6(e) to Use Alternate Notice of Interpreter Availability Posters

President Weisser provided that existing board regulations require pharmacies to prominently post the "Notice to Consumers" required by 16 CCR Section 1707.6. In addition, Section 1707.6(c) requires every pharmacy to post or provide a "point to your language" notice so that consumers are aware that interpreter services will be provided to them at no cost. That subdivision specifies that the pharmacy shall use the standardized notice provided by the board unless the pharmacy has received prior approval of another format or display methodology. The board has delegated to the Communication and Public Education Committee the authority to act on all requests to use another format or display methodology of these posters.

At the October 7, 2013 meeting, the committee considered and denied two requests to use an alternate format notice of interpreter availability. One request was from Costco, and the other from Walmart Stores (for both Walmart and Sams Club pharmacies). While each request specified additional languages (in addition to the 12 mandated by board regulation), neither contained the specific language/phrasing that is required by 16 California Code of Regulations

Section 1707.6(c): “Point to your language. Interpreter services will be provided to you upon request at no cost.” Copies of the alternate format notices considered by the committee are provided in Attachment 2.

The committee concluded that it would like to see any alternate format notice submitted for the committee’s approval to include the statement “This notice is required to be posted by the California Board of Pharmacy.”

Board staff drafted a form that can be used for future waiver requests for the committee’s consideration. Staff will add to that request form a reminder that any alternative format notice must contain the language required by 1707.6(c).

Discussion

There were no comments from the board or from the public.

c. Update on the Status of the Updated Emergency Contraception Fact Sheet, as Required by Title 16, California Code of Regulations Section 1707.5(e)

President Weisser reported that staff is in the process of securing bids to have the emergency contraception fact sheet (required by 16 CCR Section 1746(b)) translated into six languages: Chinese, Korean, Russian, Spanish, Tagalog and Vietnamese. These are the same six languages that the board makes available for its “Notice to Consumers” posters. When available, the fact sheets will be available upon request, and will also be available for download from the board’s web site. A copy of the updated emergency contraception fact sheet (English version) was provided in the meeting materials.

Discussion

There were no comments from the board or from the public.

d. Results of Assessment of California’s Patient-Centered Labeling Requirements as Required by Title 16 California Code of Regulations Section 1707.5(e)

Background

Title 16 CCR Section 1707.5 specifies requirements for patient-centered labels for prescription drug containers. When the board promulgated these requirements, it included in subdivision (e) a requirement that the board re-evaluate the requirements by December 2013 to ensure optimal conformance with Business and Professions Code Section 4076.5.

Since April 2013, the committee has initiated review of the components in the current regulatory requirements. President Weisser noted that the USP guidelines for prescription container labeling published in November 2012 had a close resemblance to the board’s requirements.

Ms. Herold stated that staff continues to search for medical literacy research regarding standardized directions for use, noting the goal of such a schedule is to increase patient understanding, adherence to medication instructions and improving health outcomes. Board staff has been trying to build support among groups by highlighting the benefits of using standardized directions for use, and that there may be educational opportunities to work with the other prescribing boards to this end.

One of the recommendations in the NCPDP's White Paper is to implement the use of universal medication instructions in an effort to help standardize e-prescribing directions for use. In its various surveys regarding components of the patient-centered labels, the board has looked at the use of font sizes, how interpretive services requirements are being implemented, and patient satisfaction with labels – noting they want larger font, and the purpose on the label.

At the October 7, 2013 committee meeting, the committee discussed the distribution of the surveys, noting that CPEHN distributed the board-translated surveys among limited English and other groups to secure their input.

Board Meeting Discussion

President Weisser reported that at the October 7, 2013 committee meeting, the committee discussed what should be considered “patient-centered.” Regulations currently require that “patient-centered” items (listed below) shall be clustered into one area of the label that comprises at least 50 percent of the label:

1. Name of the patient
2. Name of the drug and strength of the drug
3. The directions for use
4. The condition or purpose, if it is indicated on the prescription.

The committee discussed and recommended that these four items, and specifically only these four items, remain clustered into the one area of the label that comprises at least 50 percent of the label in at least 10 point font (or 12 point if requested).

President Weisser provided that the committee also discussed if changes should be made to 1707.5(a)(1)(B) regarding the “name of the drug and strength of the drug.” The committee recommended that Section 1707.5(a)(1)(B) be modified to remove the requirement that the manufacturer be in the “patient-centered” clustered items. They also recommended amending the language where a generic is dispensed to say “generic for” (the trade name). Staff worked with counsel to develop the following language. Laura add the language here.

At the October 7, 2013 committee meeting, the committee also discussed if purpose or condition should be on the patient-centered portion of the label. President Weisser reported that there was strong consensus among the committee and the public at the meeting that the

purpose or condition should be on the prescription label within the clustered patient-centered items. Currently the purpose is only required to be on the label if it is specified on the prescription. The committee directed staff to work with legal counsel to draft language to amend Section 1707.5(a) (1)(D) to allow the purpose or condition to be included in the patient-centered clustered items.

Acknowledging the Governor's recent veto of legislation (SB 205) that sought to mandate a 12-point font on prescription labels, the board discussed the current font requirements in the regulation.

President Weisser reported that staff summarized surveys which indicated that pharmacies, by a wide preponderance, are currently using 12 point font as the primary font on prescription labels. It was the consensus of the committee that the regulation should be modified to require a minimum 12 point font. The committee recommended modifying Section 1707.5(a)(1) to read as follows:

(1) Each of the following items shall be clustered into one area of the label that comprises at least 50 percent of the label. Each item shall be printed in ~~at least a 10-point sans serif typeface or, if requested by the consumer,~~ at least a 12-point sans serif typeface, and listed in the following order:

There was substantial discussion of this and other elements of the patient-centered regulations by the board and the public. President Weisser and staff counsel asked that each of the committee recommendations be discussed and voted on separately.

Ms. Herold noted that in the Governor's veto message for SB 205 he stated that rather than mandate a statutory change to establish a minimum font size on prescription labels, he would wait for the Board of Pharmacy to finish its review of its patient-centered label regulations.

Ms. Veale commented that she has no issue with the 12 point font, however she expressed concern that requiring the patient-centered portion to be 50 percent of the label would not leave enough room for other information such as number of refills. President Weisser commented that in the surveys he did not see that there was a concern with refills being printed in too small a font. Ms. Herold added that she does recall anyone saying the four items that are considered "patient centered" are not the most important information for patients and caregivers. The goal has been to keep the portion of the label containing those four items as uncluttered as possible. Ms. Herold added that overall the feedback received by the board mainly focused on making the font for the patient-centered items as large as possible.

Mr. Lippe commented that an issue that had been previously discussed is what to do if the directions for use are very long. He asked if that had been resolved. Ms. Herold responded that Board Member Wong brought in samples of labels he uses in his pharmacy which have long directions for use, where he was able to make fit this fit within the 50 percent space.

Ms. Wheat commented that she is opposed to the committee recommendation because the sample size that of the surveys received was so small that the board should not take action based on the results. Ms. Wheat added that she does not feel the board needs to change the law to require 12 point font as patients are able to get 12 point font if they request it.

Mr. Law commented he is uncertain if the board really needs to assign a specific percentage requirement for the patient-centered area of the label.

Dr. Castellblanch and Ms. Shellans again asked that the board discuss and vote on each recommendation separately to avoid confusion.

Dr. Wong commented that the market will regulate itself so the board does not have to create regulations that may perhaps be unnecessary.

Ms. Herold stated that this regulation was very controversial from the beginning and that is why the board agreed to review the regulation in two years. The public *strongly* requested 12 point font. Ms. Herold added that the board does not have to decide on everything at this meeting, if additional items need to be considered such as the 50 percent requirement, it can be placed on a future agenda.

Ms. Wheat commented that the law is working as it is, people are asking 12 point font and they are getting it. She does not feel that the board needs to change it just because people ask.

President Weisser reminded the board and the public that the board will take each committee recommendation for discussion and voting.

Amend Section 1707.5(a)(1) to read as follows, to specify that only the four items listed in that paragraph are to be within the patient-centered clustered area.

(1) Each of the following items, **and only these four items**, shall be clustered into one area of the label that comprises at least 50 percent of the label. Each item shall be printed in at least a 10-point sans serif typeface or, if requested by the consumer, at least a 12-point typeface, and listed in the following order:

1. Name of the patient
2. Name of the drug and strength of the drug
3. The directions for use
4. The condition or purpose, if it is indicated on the prescription.

Mandy Lee, from the California Retailer's Association, commented that the board seemed to be discussing multiple recommendations at once and asked for clarification on what the board was voting to change. President Weisser responded that currently the board is voting on adding the phrase "and only those four items" to the regulation. Ms. Shellans noted that there would not

be any adoption at this meeting, the board would just be deciding if they want to move in that direction and possibly initiate the rulemaking.

Dr. Castellblanch stated that he thought that if the board voted on the committee recommendations it would move to rulemaking today. He added that many people have shown up to this meeting specifically to give comments on patient-centered labels.

Mandy Lee, from the California Retailers Association, commented that prescription bottle labels are one of the most over regulated pieces in pharmacy and she cautioned the board from adding additional requirements.

Committee Recommendation: Amend Section 1707.5(a)(1) to read as follows, to specify that only the four items listed in that paragraph are to be within the patient-centered clustered area.

- 1707.5(a)(1) Each of the following items, **and only these four items**, shall be clustered into one area of the label that comprises at least 50 percent of the label. Each item shall be printed in at least a 10-point sans serif typeface or, if requested by the consumer, at least a 12-point typeface, and listed in the following order:
- A. Name of the patient
 - B. Name of the drug and strength of the drug. For the purposes of this section, name of the drug” means either the manufacturer’s trade name of the drug, or the generic name and the name of the manufacturer.
 - C. The directions for use
 - D. The condition or purpose, if it is indicated on the prescription.

Support: 10 Oppose: 1 Abstain: 0

President Weisser moved the discussion to the next committee recommendation which was the removal of the requirement that the manufacturer be in the “patient-centered” clustered items (knowing the manufacturer name will be elsewhere on the label); and amending the language where a generic is dispensed to say “generic for” (the trade name).

Ms. Herold commented that at a previous meeting someone gave a very clear example of a patient who had been given a brand name drug and they already had a generic at home. The patient did not realize it was the same medication and took both. The proposed amendment would address this issue, and help prevent such a mistake.

Mr. Room pointed out that the language that was given to the board did not include the “generic for” section, so it would need to be added before a vote could be taken.

Mr. Zee commented that due to some of the language being missing he would like to table the motion until the board could receive complete language clearly showing what was being added and removed.

Dr. Castellblanch asked if Mr. Zee wanted to table just this particular committee recommendation or the entire patient centered label discussion. Mr. Zee responded that he would like to table the entire patient centered discussion for a future meeting.

Dr. Castellblanch commented that the board noticed to the public that the patient-centered labels would be discussed at this meeting. He expressed his opinion that it is the board's responsibility to take action on items that have been properly noticed.

Mandy Lee commented that she would support Mr. Zee's motion to table the entire discussion.

Carrie Sanders, from the Pan Ethnic Health Network, commented she had traveled to the meeting from the Bay Area specifically for the patient-centered label discussion.

Donna Hernandez, from the California Alliance of Retired Americans, commented that many of their members traveled a long way to be at the meeting and she asked the board to continue their discussion.

Jonathan Nelson, from the California Society of Health System Pharmacists, supported Mr. Zee's motion.

Dr. Castellblanch again expressed his desire for the board to continue with the discussion rather than tabling it for future meetings.

Ms. Wheat added that she supported Mr. Zee's motion to table the entire patient-centered label discussion until proper language could be provided at a future meeting.

Motion: Table the discussion regarding the entire patient centered label regulation because of the problems and inconsistencies in the language provided to the board.

M/S: Zee/Wheat

Support: 4 Oppose: 7 Abstain: 0

As the motion to table the discussion failed, Mr. Room reported that he had been able to create language for the board and public to view on the projector screen. While the language was being put on the projector he recommended that the board move to the next committee recommendation – 12 point font.

President Weisser moved the discussion to the next committee recommendation: Each item shall be printed in 12-point sans serif typeface.

Dr. Castellblanch commented that the U.S. Pharmacopeia has recommended a national standard of 12 point font and the public has been very vocal in their support of 12 point font.

Ms. Wheat commented that she feels the law currently allows for flexibility in choosing whether to use 10 or 12 point font and she would not support the motion to require 12 point font only.

Ms. Don Braun Seema, from the California Alliance for Retired Americans, expressed her support for requiring 12 point font.

Ms. Pat Stanyo, from the California Alliance for Retired Americans, commented that she supports the committee recommendation to require 12 point font as many people do not realize that currently they have to request it if they need it.

Donna Hernandez, from the California Alliance for Retired Americans, expressed her support for 12 point font as well as having the purpose on the label.

Lorenzo Reals, from California Alliance for Retired Americans, commented that some of his friends have gone to pharmacies that refuse to provide larger font, so the 12 point requirement is necessary. President Weisser responded that any time someone goes into a pharmacy and finds that they are violating pharmacy law, the patient should file a complaint so the board can investigate.

A representative from Peoples Pharmacy commented that fitting all the ingredients for a compounded medication in 12 point font would be nearly impossible.

Sharron Nacamoto, from California Alliance for Retired Americans, commented that she supports the 12 point font.

Al Carter, from Walgreens, asked if the “generic for” would need to be in 12 point font. Ms. Herold responded that it would.

Carrie Sanders, from the Pan Ethnic Health Network, stated that the network strongly supports the use of 12 point font.

Mandy Lee, from the California Retailers Association, asked the board to consider allowing a year or two time period for all of their members to get in compliance with the 12 point font requirement if it passed today. Mr. Zee asked how long the members would need. Ms. Lee commented that they would need a year or two. Ms. Herold responded that even if the board finalized the regulation today the earliest they get the regulation in place would be at least a year, if not longer.

Committee Recommendation: Modify Section 1707.5(a)(1) to read as follows:

1707.5(a)(1) Each of the following items, and only these four items, shall be clustered into one area of the label that comprises at least 50 percent of the label. Each item shall be printed ~~in at least a 10-point sans serif typeface or, if requested by the consumer,~~ at least a 12-point sans serif typeface, and listed in the following order:

- A. Name of the patient
- B. Name of the drug and strength of the drug. For the purposes of this section, name of the drug” means either the manufacturer’s trade name of the drug, or the generic name and the name of the manufacturer.
- C. The directions for use
- D. The condition or purpose, if it is indicated on the prescription.

Support: 10

Oppose: 1

Abstain: 0

Dr. Gutierrez thanked the public for attending the meeting and providing feedback.

President Weisser indicated that the board would now move back to the previous committee recommendation to modify Section 1707.5(a)(1)(B) to remove the requirement that the manufacturer be in the “patient-centered” clustered items (knowing the manufacturer name will be elsewhere on the label); and amend the language where a generic is dispensed to say “generic for” (the trade name).

Mr. Room had been able to finalize the language on the “generic for” section of the language. The language Mr. Room created was displayed on the projector screen so the board and the public could view it. The language was displayed as follows:

1707.5(a)(1)(B)

Name of the drug and strength of the drug. For the purposes of this section, “name of the drug” means ~~either~~ the manufacturer’s trade name of the drug or, if a generic is dispensed, or the generic name of the ~~manufacturer~~ drug and a parenthetical containing “generic for” and the trade name of the drug.

Mr. Lippe commented that the pharmacy he goes to already does this.

Ms. Veale expressed her opinion that the manufacturer is a very important piece of information asked that the public provide feedback if the removal of the manufacturer from the patient-centered label would be a problem.

Dr. Gutierrez clarified that the manufacturer would still be on the label, it would just not be in the patient-centered portion.

Dr. Wong commented that he feels the manufacturer should remain in the patient-centered section of the label, right next to the drug name.

Donna Hernandez, from the California Alliance for Retired Americans, asked to clarify if “manufacturer” means the company who making the drug not the generic name of the drug. Mr. Room confirmed this. Ms. Hernandez replied that she does not think manufacturer is important enough to be in the patient-centered portion of the label as long as the generic name was there.

Lorenzo Reals, from California Alliance for Retired Americans, commented that he does not feel the language needs to be changed at all.

Dennis McAllister, from Express Scripts, agreed with Mr. Reals that the current language is good enough.

Carrie Sanders, from the Pan Ethnic Health Network, expressed her support of listing both the brand name and generic name.

Al Carter, from Walgreens, stated that manufacturer should remain in the same location on the label.

Megan Harwood, from San Gabriel Medical Pharmacy, commented that listing the manufacturer right next to the drug name may actually confuse the public.

Mr. Room clarified that this committee recommendation would actually accomplish two things. First it would require that you provide the trade name of the drug if you are substituting a generic. The second is it eliminates the requirement for the manufacturer’s name to be included in the cluster on the patient-centered portion of the label. The manufacture’s name would still be provided in another location of the label. President Weisser added that the “generic for” information *would* be in the patient centered portion of the label.

Ms. Wheat asked to clarify if the law currently requires the use of both the manufacturer name and the generic name. Mr. Room responded that currently if you use a generic, you have to list the manufacturer; if you do not use a generic you, do not have to list the manufacturer. Ms. Wheat asked if currently you have to list the brand name if you use a generic. Mr. Room responded that currently you are *not* required to list both the brand name and generic name.

Dr. Wong asked if a doctor writes the prescription for the generic, does the label need to list both the brand name and generic name? Mr. Room responded that the proposed language would require both to be listed.

Dr. Wong asked whether a pharmacist could list the manufacturer's name as well as the generic and brand name. Mr. Room replied that the manufacturer's name could not be in the patient centered portion of the label, it would have to be provided in another section of the label.

Dr. Wong asked why it is a problem to list the manufacturer in the patient centered portion of the label. Mr. Room responded that as the board moved toward requiring 12 point font the idea was to eliminate any information that was not needed to avoid cluttering the patient centered portion. Ms. Herold added that the board also considered the value of the information to the patient, often time the manufacturer's name is abbreviated and the patient has trouble understanding what the abbreviation means.

Jonathan Nelson, from the California Society for Health System Pharmacists, commented that the board should return this item to the committee to allow for further comments from the public.

Mandy Lee, from the California Retailers Association, agreed with Mr. Nelson's comments and again asked the board to allow for a one year buffer period once the rulemaking is finalized.

Ms. Veale asked to table this specific motion and to allow time for more comments from stakeholders. Ms. Herold provided that the regulation cannot move forward until the board votes on this item.

Dr. Gutierrez commented that it makes sense for the entire regulation to be modified and implemented at one time.

Motion: Table the motion to modify Section 1707.5(a)(1)(B) to remove the requirement that the manufacturer be in the "patient-centered" clustered items (knowing the manufacturer name will be elsewhere on the label); and amend the language where a generic is dispensed to say "generic for" (the trade name).

M/S: Veale/Hackworth

Support: 8

Oppose: 3

Abstain: 0

Mr. Zee asked if the all of the changes to 1707.5 would be in one regulation package. Ms. Herold confirmed that all of the changes should be handled in one regulation.

Upon Mr. Lippe's request, Ms. Herold provided the board with an overview of the regulation process. Mr. Lippe commented that Mandy Lee's request for a one year buffer period after the regulation is finalized to allow time for implementation seemed reasonable and asked for a motion to be made to allow for it. Ms. Shellans responded that until the board has a *complete* regulation package and agrees to adopt the regulation they should not make any motion to allow for implementation time.

President Weisser clarified that in light of the motion being tabled the recommendation to remove the requirement that the manufacturer be in the “patient-centered” clustered items (knowing the manufacturer name will be elsewhere on the label); and amend the language where a generic is dispensed to say “generic for” (the trade name) would be sent back to the committee.

Mr. Room recommended that the committee recommendation to amend Section 1707.5(a) (1)(D) to allow the purpose or condition to be included in the patient-centered clustered items also be sent back to the committee. President Weisser agreed that this item would be sent back to the committee.

e. Discussion and Possible Action to Initiate a Rulemaking to Amend Title 16 California Code of Regulations Section 1707.5

As a result of the board’s discussion, the board will not be initiating a rulemaking to amend Title 16 California Code of Regulations Section 1707.5.

f. Update on *The Script*

President Weisser reported that the next issue of *The Script* is being finalized and prepared for being posted online. Staff leaves of absences and other issues have delayed the publication, but it should be available by the end of the October.

g. Public Outreach Activities Conducted by the Board

President Weisser encouraged the board and the public to review the public outreach activities provided in the meeting materials.

h. Update on the Development of Committee Goals for 2012-2017 to Fulfill the Board’s Strategic Plan

President Weisser noted that staff has suggested that at a future meeting, the committee augment its goals for the Strategic Plan.

The board recessed for break at 11:42 p.m. and resumed at 12:00 p.m.

Background and Research on Patient Centered Labels

Background and Research on Patient-Centered Prescription Container Labels

The following information has been presented to the committee and board multiple times. In the interests of providing it as a ready reference, it is being provided as an attachment to the committee meeting materials.

a. United States Pharmacopeia Guidelines for Prescription Drug Labels

In November 2012, the U.S. Pharmacopeial Convention (USP) published guidelines for prescription container labeling (**Attachment 5a**). The guidelines provide a universal approach to the format, appearance, content and language of instructions for medicines in containers dispensed by pharmacies. Review of the material in USP's guidelines would be one source of information useful for comparison of the board's regulations with guidelines for premium presentation and focus on patient needs. It is important to note that USP's guidelines already closely resemble the board's existing regulation requirements for patient-centered prescription container labels, specifically:

- Organize the prescription label in a patient-centered way. Feature the information patients most often seek out or need to understand about taking the medication safely.
 - Emphasize: directions
 - At the top of the label place: patient's name
 - Drug name (spell out full brand AND generic name)
 - Strength
 - Explicit and clear directions for use in simple language
- Prescription directions should follow a standard format so the patient can expect where to find information.
- Less critical information can be placed elsewhere and in a matter where it will not "supersede" critical patient information, and away from where it can be confused with dosing instructions
- Use language that it is clear, simplified, concise and familiar, and in a standardized manner. Use common terms and full sentences. Do not use unfamiliar words, Latin terms or medical jargon
- Use simplified, standardized sentences that have been developed to ensure ease understanding the directions (by seeking comment from diverse consumers)
- Separate dose from the timing of each dose to clearly explain how many pills to take and specify if there is an appropriate time to take them (morning, noon, evening, bedtime).
- Do not use alphabetic characters for numbers (not in CA's) e.g., "nine" instead of "9".
- Use standardized directions whenever possible.
- Avoid ambiguous terms such as "take as directed" (not in CA's) unless clear and unambiguous supplemental instructions and counseling are provided

- Include purpose on the label unless patient does not want it, and if used, use “purpose for use” language such as for blood pressure rather than hypertension.
- Limit auxiliary information, and only if evidence based. (not in CA’s)
- Use icons only if vetted with the general public (not in CA’s)
- Address limited English proficiency.
- Labels should be designed so they are easy to read. Optimize typography by using:
 - High contrast print (black print on white background)
 - Large font sizes in simple, uncondensed fonts in at least 11 point if Arial, or 12 point if Times New Roman)
 - Optimize use of white space between lines (25-30 percent of font size)
 - Horizontal placement of lettering only
 - Sentence case
 - Highlighting, bolding and other typographical cues should enhance patient-centered information, but limit the number of colors used for highlighting
- Address visual impairment (not in CA’s)

Regarding addressing limited English speaking/reading patients, USP encourages directions for use in the patient’s language as well as in English. Translations should be developed using high quality translation processes (CA’s translated directions would fit this criterion).

b. Medical Literacy Research

The National Council for Prescription Drug Programs developed the “Universal Medication Schedule White Paper” (draft April 2013, **Attachment 5b**). This document supports the standardized directions in the board’s regulation at 16 CCR Section 1707.5. The goal of the universal medication schedule is to increase patient understanding and adherence to medication instructions by standardizing the phrasing of directions, thereby improving health outcomes.

The hope is to secure the use of directions for use in a Universal Medication Schedule into e-prescribing systems. Staff will continue to identify additional medical literacy research for the committee’s consideration.

c. Surveys

The board has conducted surveys to assess California’s patient-centered label requirements. Survey results are provided in **Attachment 5c**.

1. Survey of Patient-Centered Labels in Use in California Pharmacies

The first survey was conducted in 2012 and was used to measure pharmacies' compliance with the patient-centered label requirements. It included components related to the 10- and 12-point fonts used on labels and how pharmacies have been complying with the interpreter requirements. Over the course of approximately seven months, board inspectors collected prescription labels used in California 767 pharmacies to determine compliance with the patient-centered label requirements. In general, nearly 70 percent of the labels in use as found by the board's inspectors are printed in 12-point font; 15 percent use both 10 and 12 point font on the labels; and about 15 percent are printed in 10 point.

2. Survey of Pharmacies' Compliance with Interpreter Availability

During the inspections described in the above survey in item 1, the board's inspectors also inquired how pharmacies are complying with the requirements for the availability of interpreters to provide services to limited English speaking patients. Most rely upon telephone services to provide the wide array of languages that could be needed in a language diverse state such as California. Often, staff was available to translate in communities where a language other than English is principally spoken.

3. Consumer Satisfaction with Prescription Labels

The board conducted a survey in 2012 to determine if consumers were satisfied with their prescription labels and how they could be improved. Several consumer groups including AARP, Consumers Union, and California Pan Ethnic Health Network (CPEHN) distributed the survey electronically. The survey was also translated into Chinese and Spanish by the board and distributed by CPEHN to the appropriate audiences. Further, surveys were distributed and collected in person at local Senior Scam Stopper seminars (public protection fairs) sponsored by the Contractors State License Board. The board received a total of 1204 completed surveys.

4. Survey of Pharmacies that Translate Labels

The board has surveyed pharmacies to determine if they are providing consumers with translated labels, and if they are using the translated "directions for use" that are on the board's website. A copy of the survey questions are provided in **Attachment 5d**.



FOR IMMEDIATE RELEASE

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First Universal Standards Guiding Content, Appearance of Prescription Container Labels to Promote Patient Understanding of Medication Instructions

Nearly Half of Patients Misunderstand One or More Dosage Instructions Pharmacies Across the Country Urged to Adopt "Patient-Centered" Labels

Rockville, Md., October 9, 2012 — With medication misuse resulting in more than one million adverse drug events per year in the United States, new standards released today by the U.S. Pharmacopeial Convention (USP) for the first time provide a universal approach to the format, appearance, content and language of instructions for medicines in containers dispensed by pharmacists. Wide variability in prescription container labels exists today across individual prescriptions, pharmacies, retail chains and states. The USP standards provide specific direction on how to organize labels in a "patient-centered" manner that best reflects how most patients seek out and understand medication instructions.

"Lack of universal standards for labeling on dispensed prescription containers is a root cause for patient misunderstanding, non-adherence and medication errors," said Joanne G. Schwartzberg, M.D., director, aging and community health for the American Medical Association and a member of the USP Nomenclature, Safety and Labeling Expert Committee, the group of independent experts responsible for the new standard. "With an aging and increasingly diverse population, and people utilizing a growing number of medications, the risks are more pronounced today than ever. These USP standards will promote patient understanding of their medication instructions, which is absolutely essential to preventing potentially dangerous mistakes and helping to ensure patient health and safety."

Studies have found that 46 percent of patients misunderstood one or more dosage instructions on prescription labels. The problem is particularly troublesome in patients with low or marginal literacy (one study showed patients with low literacy were 34 times more likely to misinterpret prescription warning labels), and in patients receiving multiple medications that are scheduled for administration using unnecessarily complex, non-standardized time periods. However, even patients with adequate literacy often misunderstand common prescription directions and warnings.

The USP effort to create these new standards developed from an Institute of Medicine (IOM)-led initiative to improve health literacy, which is defined as the degree to which people can obtain, process and understand the basic health information and services they need to make appropriate health decisions. According to IOM, 77 million Americans have limited health literacy, and a majority of Americans have difficulty understanding and using currently available health information and services.

Elements of the new USP standards, contained in General Chapter <17> *Prescription Container Labeling*, of the *United States Pharmacopeia* and the *National Formulary*, include:

- **Emphasize instructions and other information important to patients.** Prominently display information that is critical for patients' safe and effective use of the medicine. At the top of the

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label specify patient name, drug name (spell out full nonproprietary and brand name) and strength, and clear directions for use in simple language. Less critical information (e.g., pharmacy name, drug quantity) should not supersede critical information and should be placed away from dosing instructions.

- **Improve readability.** Labels should be designed and formatted so they are easy to read. Typography should be optimized by using high contrast print; adequate white space between lines of text (i.e., 25-30 percent of the point size); simple uncondensed familiar fonts (Times Roman or Arial are specifically recommended); and large font size (e.g., minimum 12-point Times Roman or 11-point Arial) for critical information. Older adults, in particular, have difficulty reading small print.
- **Give explicit instructions.** Instructions for use should clearly separate the dose itself from the timing of each dose. Do not use alphabetic characters for numbers. For example, write, “Take 2 tablets in the morning and 2 tablets in the evening” rather than “Take 2 tablets twice daily.” Dosing intervals such as “twice daily,” “3 times daily,” or hourly intervals such as “every 12 hours” should be avoided because such instructions are implicit rather than explicit, may involve numeracy skills, and patient interpretation may vary from prescriber intent. Although instructions worded in terms of specific hourly times (e.g., 8 a.m. and 10 p.m.) may be assumed to be more easily understood, in actual use they are less readily understood and may present greater adherence issues due to individual lifestyle patterns (e.g., shift work) than general timeframes such as “in the morning” or “after breakfast.” Ambiguous directions such as “take as directed” should be avoided without clear supplemental information.
- **Include purpose for use.** If the purpose of the medication is included on the prescription, it should be included on the label unless a patient prefers that it not appear. Confidentiality and FDA approval for intended use (i.e., labeled vs. off-label use) may cause some to constrain its inclusion on labels. Current evidence supports inclusion of purpose-for-use language in clear, simple terms, e.g., “for high blood pressure” rather than “for hypertension.”
- **Address limited English proficiency.** Whenever possible, the directions for use on a prescription container label should be provided in the patient’s preferred language. The drug name shall be in English as well so that emergency personnel can have quick access to the information. Translations should be produced using a high-quality translation process; an example is provided in the standard.
- **Address visual impairment.** Provide alternative access for visually impaired patients (e.g., tactile, auditory, or enhanced visual systems that may employ advanced mechanics or assistive technology).

“Patients’ best—and often only—source of information regarding the medications they have been prescribed is on the prescription container label,” Dr. Schwartzberg noted. Although other written information and oral counseling may be available, the prescription container label must fulfill the professional obligations of the prescriber and pharmacist. These include giving the patient the most essential information needed to understand how to safely and appropriately use the medication and to adhere to the prescribed medication regimen.

USP issued a draft version of this standard for public review and comment by all interested stakeholders—including healthcare practitioners, retailers, software vendors, consumers and others—in December 2011. The final standard will be published in November 2012, and incorporates multiple additions based on comments received, including more detail on producing high-quality translations,



the visual impairment section, and the direction to include both brand and nonproprietary names on labels.

Enforcement of the standard will be the decision of individual state boards of pharmacy, which may choose to adopt it into their regulations—similar to USP standards for sterile and nonsterile pharmaceutical compounding, both of which are widely recognized by states. At its 2012 annual meeting, the National Association of Boards of Pharmacy passed a resolution supporting state boards in requiring a standardized prescription container label.

Examples of prescription container labels that comply with the new USP standard are available at <http://uspgo.to/prescription-container-labeling>. Media inquiries may be directed to mediarelations@usp.org.

###

USP – Advancing Public Health Since 1820

The United States Pharmacopeial Convention (USP) is a scientific, nonprofit, standards-setting organization that advances public health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods. USP's standards are relied upon and used worldwide. For more information about USP visit <http://www.usp.org>. FY1317

Add the following:

◀(17) PRESCRIPTION CONTAINER LABELING

INTRODUCTION

Medication misuse has resulted in more than 1 million adverse drug events per year in the United States. Patients' best source (and often only source) of information regarding the medications they have been prescribed is on the prescription container label. Although other written information and oral counseling sometimes may be available, the prescription container label must fulfill the professional obligations of the prescriber and pharmacist. These obligations include giving the patient the most essential information needed to understand how to safely and appropriately use the medication and to adhere to the prescribed medication regimen.

Inadequate understanding of prescription directions for use and auxiliary information on dispensed containers is widespread. Studies have found that 46% of patients misunderstood one or more dosage instructions, and 56% misunderstood one or more auxiliary warnings. The problem of misunderstanding is particularly troublesome in patients with low or marginal literacy and in patients receiving multiple medications that are scheduled for administration using unnecessarily complex, nonstandardized time periods. In one study, patients with low literacy were 34 times more likely to misinterpret prescription medication warning labels. However, even patients with adequate literacy often misunderstand common prescription directions and warnings. In addition, there is great variability in the actual auxiliary warning and supplemental instructional information applied by individual practitioners to the same prescription. The specific evidence to support a given auxiliary statement often is unclear, and patients often ignore such information. The essential need for, and benefit of, auxiliary label information (both text and icons) in improving patient understanding about safe and appropriate use of their medications vs. explicit simplified language alone require further study.

Lack of universal standards for labeling on dispensed prescription containers is a root cause for patient misunderstanding, nonadherence, and medication errors. On May 18, 2007, the USP Safe Medication Use Expert Committee established an Advisory Panel to: 1) determine optimal prescription label content and format to promote safe medication use by critically reviewing factors that promote or distract from patient understanding of prescription medication instructions and 2) create universal prescription label standards for format/appearance and content/language.

In November 2009, the Health Literacy and Prescription Container Labeling Advisory Panel presented its recommendations to the Safe Medication Use Expert Committee, which then requested that USP develop patient-centered label standards for the format, appearance, content, and language of prescription medication instructions to promote patient understanding. These recommendations form the basis of this general chapter.

Note—These standards do not apply when a prescription drug will be administered to a patient by licensed personnel who are acting within their scope of practice.

PRESCRIPTION CONTAINER LABEL STANDARDS TO PROMOTE PATIENT UNDERSTANDING

Organize the prescription label in a patient-centered manner: Information shall be organized in a way that best reflects how most patients seek out and understand medication instructions. Prescription container labeling should feature only the most important patient information needed for safe and effective understanding and use.

Emphasize instructions and other information important to patients: Prominently display information that is critical for patients' safe and effective use of the medicine. At the top of the label specify the patient's name, drug name (spell out full generic and brand name) and strength, and explicit clear directions for use in simple language.

The prescription directions should follow a standard format so the patient can expect that each element will be in a regimented order each time a prescription is received.

Other less critical but important content (e.g., pharmacy name and phone number, prescriber name, fill date, refill information, expiration date, prescription number, drug quantity, physical description, and evidence-based auxiliary information) should not supersede critical patient information. Such less critical information should be placed away from dosing instructions (e.g., at the bottom of the label or in another less prominent location) because it distracts patients, which can impair their recognition and understanding.

Simplify language: Language on the label should be clear, simplified, concise, and familiar, and should be used in a standardized manner. Only common terms and sentences should be used. Do not use unfamiliar words (including Latin terms) or medical jargon.

Use of readability formulas and software is not recommended to simplify short excerpts of text like those on prescription labels. Instead, use simplified, standardized sentences that have been developed to ensure ease of understanding the instructions correctly (by seeking feedback from samples of diverse consumers).

Give explicit instructions: Instructions for use (i.e., the SIG or signatur) should clearly separate the dose itself from the timing of each dose in order to explicitly convey the number of dosage units to be taken and when (e.g., specific time periods each day such as morning, noon, evening, and bedtime). Instructions shall include specifics on time periods. Do not use alphabetic characters for numbers. For example, write "Take 2 tablets in the morning and 2 tablets in the evening" rather than "Take two tablets twice daily".

Whenever available, use standardized directions (e.g., write "Take 1 tablet in the morning and 1 tablet in the evening" if the prescription reads b.i.d.). Vague instructions based on dosing intervals such as twice daily or 3 times daily, or hourly intervals such as every 12 hours, generally should be avoided because such instructions are implicit rather than explicit, they may involve numeracy skills, and patient interpretation may vary from prescriber intent. Although instructions that use specific hourly times (e.g., 8 a.m. and 10 p.m.) may seem to be more easily understood than implicit vague instructions, recommending dosing by precise hours of the day is less readily understood and may present greater adherence issues due to individual lifestyle patterns, e.g., shift work, than more general time frames such as in the morning, in the evening, after breakfast, with lunch, or at bedtime. Consistent use of the same terms should help avoid patient confusion.

Ambiguous directions such as "take as directed" should be avoided unless clear and unambiguous supplemental instructions and counseling are provided (e.g., directions for use that will not fit on the prescription container label). A clear statement referring the patient to such supplemental materials should be included on the container label.

Include purpose for use: If the purpose of the medication is included on the prescription, it should be included on the prescription container label unless the patient prefers that it not appear. Always ask patients their preference when prescriptions are submitted for filling. Confidentiality and FDA approval for intended use (e.g., labeled vs. off-label use) may limit inclusion of the purpose on labels. Current evidence supports inclusion of purpose-for-use language in clear, simple terms (e.g., "for high blood pressure" rather than "for hypertension").

Limit auxiliary information: Auxiliary information on the prescription container label should be evidence-based in simple explicit language that is minimized to avoid distracting patients with nonessential information. Most patients, particularly those with low literacy, pay little attention to auxiliary information. The information should be presented in a standardized manner and should be critical for patient understanding and safe medication use (e.g., warnings and critical administration alerts). Icons are frequently misunderstood by patients. In addition, icons that provide abstract imagery for messages that are difficult to visually depict may be ineffective at improving understanding compared with simplified text alone. Use only icons for which there is adequate evidence, through consumer testing, that they improve patient understanding about correct use. Evidence-based auxiliary information, both text and icons, should be standardized so that it is applied consistently and does not depend on individual practitioner choice.

Address limited English proficiency: Whenever possible, the directions for use on a prescription container label should be provided in the patient's preferred language. Otherwise there is a risk of misinterpretation of instructions by patients with limited English proficiency, which could lead to medication errors and adverse health outcomes. Additionally, whenever possible, directions for use should appear in English as well, to facilitate counseling; the drug name shall be in English so that emergency personnel and other intermediaries can have quick access to the information.

Translations of prescription medication labels should be produced using a high-quality translation process. An example of a high-quality translation process is:

- Translation by a trained translator who is a native speaker of the target language
- Review of the translation by a second trained translator and reconciliation of any differences
- Review of the translation by a pharmacist who is a native speaker of the target language and reconciliation of any differences
- Testing of comprehension with target audience

If a high-quality translation process cannot be provided, labels should be printed in English and trained interpreter services used whenever possible to ensure patient comprehension. The use of computer-generated translations should be limited to programs with demonstrated quality because dosage instructions can be inconsistent and potentially hazard-

ous. Standardized translated instructions and technology advances are needed to ensure the accuracy and safety of prescription container labeling for patients with low English proficiency.

Improve readability: Labels should be designed and formatted so they are easy to read. Currently no strong evidence supports the superiority in legibility of serif vs. sans serif typefaces, so simple uncondensed fonts of either type can be used.

Optimize typography by using the following techniques:

- High-contrast print (e.g., black print on white background).
 - Simple, uncondensed familiar fonts with sufficient space within letters and between letters (e.g., Times Roman or Arial).
 - Sentence case (i.e., punctuated like a sentence in English: initial capital followed by lower-case words except proper nouns).
 - Large font size (e.g., minimum 12-point Times Roman or 11-point Arial) for critical information. Note that point size is not the actual size of the letter, so 2 fonts with the same nominal point size can have different actual letter sizes. X-height, the height of the lower-case x in typeface, has been used as a more accurate indicator of apparent size than point size. For example, for a given point size, the x-height and apparent size of Arial are actually bigger than those for Times Roman. Do not use type smaller than 10-point Times Roman or equivalent size of another font. Older adults, in particular, have difficulty reading small print.
 - Adequate white space between lines of text (25%–30% of the point size).
 - White space to distinguish sections on the label such as directions for use vs. pharmacy information.
 - Horizontal text only.
- Other measures that can also improve readability:
- If possible, minimize the need to turn the container in order to read lines of text.
 - Never truncate or abbreviate critical information.
 - Highlighting, bolding, and other typographical cues should preserve readability (e.g., high-contrast print and light color for highlighting) and should emphasize patient-centric information or information that facilitates adherence (e.g., refill ordering).
 - Limit the number of colors used for highlighting (e.g., no more than one or two).
 - Use of separate lines to distinguish when each dose should be taken.

Address visual impairment:

- Provide alternative access for visually impaired patients (e.g., tactile, auditory, or enhanced visual systems that may employ advanced mechanics of assistive technology).

The National Council for Prescription Drug Programs developed the “Universal Medication Schedule White Paper” (draft April 2013). This document supports the standardized directions in the board’s regulation at 16 CCR Section 1707.5. The goal of the universal medication schedule is to increase patient understanding and adherence to medication instructions by standardizing the phrasing of directions, thereby improving health outcomes.

A link to the “Universal Medication Schedule White Paper” is provided below.

<http://www.drugstorenews.com/sites/drugstorenews.com/files/NCPDP.pdf>

Summary

Patient-Centered Labeling Inspections

DATE: April - August 2012

This survey is intended to be used during inspections of all pharmacies. Unless otherwise indicated, please use tally marks. Sections 1-4 should always be completed. Section 5 will only be used if the pharmacy is compliant and indicated as such in section 4.

1	Number of Inspections	767
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2	Patient-Centered Label (B&P 4076[a] & CCR 1707.5[a][1][A] - [D])			
		Chain Store	Community	Clinic
	Compliant	355	339	1
	Noncompliant	13	67	7
	Corrections issued	13	49	7

3	The label is usually printed in...	Chain Store	Community	Clinic
	10-point font is the default	40	73	0
	12-point font is the default	280	161	1
	Both 10-point & 12-point font appear on the label	47	138	0

Please tally the number in sections 2 and 3 of the survey. This survey is designed to measure compliance with the patient-centered labeling requirements (section 2). Section 3 is designed to identify if pharmacies are defaulting to the larger or smaller font, or using a combination of sizes on the patient-centered elements.

4	Interpretative Services (CCR 1707.5[d])			
		Chain Store	Community	Clinic
	Compliant (all 12 languages available)	349	253	0
	Noncompliant	23	150	1
	Corrections issued	23	146	1

5	If compliant, interpretative services provided by	Chain Store	Community	Clinic
	Staff only	17	2	0
	Telephone (e.g. language line)	68	51	0
	Combination of staff and telephone	260	199	43
	Other, please specify	0	1	0

Please tally the number of pharmacies compliant and non-compliant in Section 4. Complete Section 5 section only if the pharmacy is compliant with the interpretative services provisions.

Other: Internal system with video conference - UC Davis

**California State Board of Pharmacy
Patient-Centered Prescription Label Survey**

Objective

To secure public comments from California consumers regarding the new patient-centered prescription labels pursuant to Senate Bill 472 (Chapter 470, Statutes of 2007).

Methodology

The consumer survey soliciting feedback regarding the readability of the new prescription drug container labels was widely distributed. An electronic version of the survey was sent to several consumer groups, who in turn distributed the survey to their ListServe contacts. The survey was also translated into Chinese and Spanish and distributed by The California Pan Ethnic Health Network (CPEHN) to the appropriate audiences. Surveys have also been collected at local Senior Scam Stopper seminars sponsored by the Contractors State Licensing Board.

Results

A total of 1204 surveys were received. Respondents did not always provide answers to all of the questions. Results are summarized below:

Responses to Yes/No Questions

English: 1142 Surveys Received	YES	NO
1. Are your prescription container labels easy to read?	693	502
2. Are the directions for taking the medicine easy to understand?	245	959
3. Do you know why you take each of your medicines?	1049	149
4. Would you like the general reason why you take the medicine to appear on the label (for pain, for infection, etc.)?	963	232

Chinese: 46 Surveys Received	YES	NO
1. Are your prescription container labels easy to read?	40	5
2. Are the directions for taking the medicine easy to understand?	45	1
3. Do you know why you take each of your medicines?	42	4
4. Would you like the general reason why you take the medicine to appear on the label (for pain, for infection, etc.)?	30	4

Spanish: 16 Surveys Received	YES	NO
1. Are your prescription container labels easy to read?	6	10
2. Are the directions for taking the medicine easy to understand?	7	9
3. Do you know why you take each of your medicines?	7	9
4. Would you like the general reason why you take the medicine to appear on the label (for pain, for infection, etc.)?	16	0

Top responses to open-ended questions:

When asked what information on the label was most important, the top responses were:

1. Directions for use/clear dosing instructions: 539 of 1098 responses = 49%
2. Name of drug (including generic and brand name): 403 of 1098 responses = 36%
3. Side effects/warnings/interactions/contraindications: 68 of 1098 responses = 6%

When asked what changes would make the labels better, the top responses were:

1. Larger font: 318 of 1180 responses = 26%
2. State purpose for taking med: 84 of 1180 responses 7%
3. Include brand name as well as generic name: 52 of 1180 responses = 4%

When asked how the information could be improved:

1. Include clear directions/dosing instructions: 123 of 574 responses = 21%
2. Larger font: 43 of 574 = 7%
3. Include purpose for taking the med: 27 of 574 = 4%

Survey Questions Regarding Translated Labels:

1. Do you provide prescription container labels with translated directions?
 - a) Yes
 - b) No (if no, go to question 4)

2. How do you provide the translation of the directions for use?
 - a) Pharmacy staff translates the labels
 - b) The pharmacy uses the Board of Pharmacy's online translated directions for use
 - c) The pharmacy uses computer software or online programs
 - d) The pharmacy uses other means of providing translations (describe):

3. If you translate the labels, do you also provide the English language equivalent on the label?
 - a) Yes
 - b) No

4. If you do not provide translated directions on the label, why?
 - a) The pharmacy has no requests for translated labels
 - b) The pharmacy has too many patients with diverse language needs
 - c) The pharmacy's software will not print in foreign language fonts
 - d) The pharmacy is concerned that errors on the label will go undetected
 - e) Other: _____

5. How does the pharmacy comply with the interpreter requirements?
 - a) Uses pharmacy staff at this or other pharmacies to interpret
 - b) Uses a telephone language service
 - c) Is not compliant with current requirements to have access to an interpreter

Inspector: _____ Date _____

Pharmacy: _____

Survey Results Regarding Pharmacy Compliance with Translated Labels and Interpreter Availability

A total of 239 surveys were collected by Board inspectors. The results are as follows:

1. Do you provide prescription container labels with translated directions?

a) Yes 185 (77.4%) b) No 54 (22.6%)

Individual Comments:

Limited Spanish

No occasion has arisen

Spanish/French Canadian on label and as counseling information

Spanish

Spanish only

2. How do you provide the translation of the directions for use?

a) Pharmacy staff translates the labels: 69 (37.3%)

Individual Comment: Spanish Only

b) The pharmacy uses the Board of Pharmacy's online translated directions for use: 5 (2.7%)

c) The pharmacy uses computer software or online programs: 151 (81.67%)

Comments: Spanish only; by Sigs only; no free-form Sigs can be translated on label.

d) The pharmacy uses other means of providing translations (describe): 12 (6.5%)

Individual Responses:

1. Third party Language Line, although the occasion has never arisen

2. Language Line

3. Store employees (Spanish only). No other language translations have ever come up

3. If you translate the labels, do you also provide the English language equivalent on the label?

a) Yes 47 (26%) b) No 134 (74%)

Individual Comments:

Optional

If the software is used correctly an additional leaflet prints in English, with label information and medication information

No room/space for both

Hard copy is in English

RPh translates based on Spanish experience

Some prescribers write both English and the foreign language, so the pharmacy puts both on the label

Has never come up

Don't use often

Don't know if label provides English translation.

4. If you do not provide translated directions on the label, why?

a) The pharmacy has no requests for translated labels 28 (51.9%)

b) The pharmacy has too many patients with diverse language needs 4 (7.4%)

c) The pharmacy's software will not print in foreign language fonts 18 (33.3%)

d) The pharmacy is concerned that errors on the label will go undetected 14 (25.9%)

e) Other:

Individual Responses:

Pharmacy has not contracted with any software vendor to provide labels yet (new pharmacy).

Pharmacy has no prescription processing software at this time (new pharmacy).

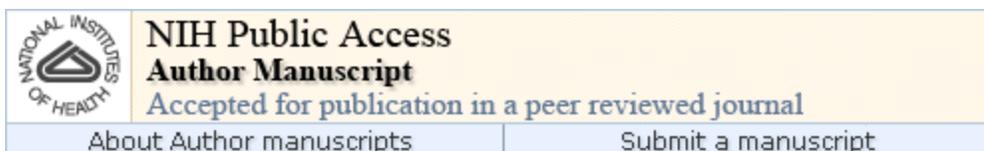
5. How does the pharmacy comply with the interpreter requirements?

- a) Uses pharmacy staff at this or other pharmacies to interpret 138 (57.7%)
- b) Uses a telephone language service 190 (77.5%)
- c) Is not compliant with current requirements to have access to an interpreter 15 (6.3%)

Individual Comments:

Is not in full compliance. Only has Spanish-speaking staff.

Both staff and rarely Language Line



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Effect of Standardized, Patient-Centered Label Instructions to Improve Comprehension of Prescription Drug Use

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Abstract

Objective

To evaluate the effectiveness of standardized, patient-centered label (PCL) instructions to improve comprehension of prescription drug use compared to typical instructions.

Methods

500 adult patients recruited from two academic and two community primary care clinics in Chicago, IL and Shreveport, LA were assigned to receive: 1) standard prescription instructions written as times per day (once, twice three times per day) [usual care], 2) PCL instructions that specify explicit timing with standard intervals (morning, noon, evening, bedtime) [PCL], or 3) PCL instructions with a graphic aid to visually depict dose and timing of the medication [PCL + Graphic]. The outcome was correct interpretation of label instructions.

Results

Instructions with the PCL format were more likely to be correctly interpreted compared to standard instructions (Adjusted Relative Risk (RR) 1.33, 95% Confidence Interval (CI) 1.25 – 1.41). Inclusion of the graphic aid (PCL + Graphic) decreased rates of correct interpretation compared to PCL instructions alone (RR 0.93, 95% CI 0.89 - 0.97). Lower literate patients were better able to interpret PCL instructions (low literacy: RR 1.39, 95% CI 1.14 – 1.68; p=0.001).

Conclusion

The PCL approach could improve patients' understanding and use of their medication regimen.

Keywords: Prescription, medication, comprehension, patient, labels, safety, health literacy

Patients frequently have difficulty correctly interpreting common prescription drug instructions,¹⁻⁵ Those with limited literacy are at greater risk for making errors in understanding how to use a specified medication. Multiple factors may contribute to misunderstanding, including unnecessarily complex and variable instructions.⁶ Recent studies have shown considerable variability in both the way that physicians write prescriptions and how pharmacies transcribe physicians' instructions.^{7,8} These problems have been highlighted in two recent Institute of Medicine (IOM) reports.^{9,10}

The Food and Drug Administration and other organizations have long sought 'best practice' standards for prescription drug labeling.¹¹⁻¹⁵ Some evidence suggests that simplified and explicit instructions can improve patient comprehension.¹⁶⁻¹⁸ In 2007, an evidence-based, patient-centered drug label design (PCL) was proposed to improve understanding and eliminate variability in clinical practice.¹⁰ The PCL sequences and organizes information on the label from a patient's perspective, and encourages prescribing medication around four standard time periods (morning, noon, evening, bedtime); a format that accounts for how nearly 90 percent of solid pill form medications are prescribed.¹⁰

We sought to evaluate whether use of PCL instructions would improve patient comprehension compared to a current, widely used standard. In addition, the use of a graphic aid accompanying the text PCL instructions that visually depicted the PCL time periods was evaluated to determine if it produced any incremental improvement in patient comprehension, particularly among those with limited literacy.¹⁹

Methods

A cross-sectional evaluation of the efficacy of PCL instructions was conducted. Patients were sequentially assigned to receive either 1) standard prescription drug label instructions [usual care], 2) labels using the PCL format and plain language instructions mapped to four standard specified time periods [PCL], or 3) labels using the PCL label instructions with an included graphic aid to visually depict dose and timing of the medication [PCL + Graphic] ([Table 1](#)).

Table 1
Prescription Label Instructions by Study Arm.

Instruction	Standard	PCL	PCL + Giv
1	Take one pill by mouth once daily	Take 1 pill at bedtime	Take 1 pill: 
2	Take one pill by mouth three times daily	Take 1 pill in the morning, 1 pill at noon, and 1 pill in the evening	Take 1 pill: and 1 pill: 
3	Take two pills by mouth	Take 2 pills in the morning, and 2 pills at	Take 2 pills: 

[Table 1](#)

Prescription Label Instructions by Study Arm.

Study Participants

Adults attending one of four outpatient clinics were recruited in Shreveport, Louisiana and Chicago, Illinois. One clinic in each city was an academic general medicine practice while a second was a community health center. Subject recruitment took place between June and August 2007. Patients were eligible if they were 18 or older, and ineligible if the clinic nurse or study research assistant (RA) identified a patient as having one or more of the following conditions: (1) severely impaired vision; (2) hearing problems; (3) too ill to participate; 4) non-English speaking. Institutional Review Boards for all locations approved the study. A total of 562 patients were approached in the order they arrived at clinics and prior to medical encounters; 530 consented to the study. In all, 500 patients participated in the study (30 patients deemed ineligible); the sample was evenly split across the two study locations (n=250 per city) and practice setting (academic, community; n=125 within each study location). A response rate of 92.8% was determined following American Association for Public Opinion Research standards.²⁰

Intervention

We tested the use of PCL instructions to help patients accurately read and dose out medication regimens at appropriately spaced intervals. Four time periods are used to identify when medicine should be taken: morning, noon, evening, and bedtime. In addition, text is simplified, numeric characters instead of words detail dose (e.g. number of pills), and ‘carriage returns’ place each dose on a separate line to clearly identify every time period a medicine is to be taken (see instructions 2 and 3, [Table 1](#)). The use of a graphic aid to visually depict the four PCL time periods and the number of pills to be taken at each time was also included and its added benefit targeted in the evaluation. The graphic was pilot tested among 50 primary care patients at the academic internal medicine practice in Chicago to confirm its feasibility.

Structured Interview and Assignment

A structured interview protocol was developed to assess patient understanding of the PCL with and without the graphic aid; a process previously used by our research team.^{3,5,16} A trained RA collected sociodemographic information, then presented patients, one at a time, with three prescription pill bottle containers with either standard, PCL, or PCL + Graphic drug labels attached for review. Subjects were exposed to only one label type. Once patients provided their

interpretations, the RA administered the Rapid Estimate of Adult Literacy in Medicine (REALM).²¹⁻²³

Outcomes

Correct interpretation of the three prescription drug label instructions was evaluated by 1) subjects' verbatim response to the RA asking “In your own words, how would you take this medicine?”, and 2) subjects' demonstration of understanding by a second question: “How many pills would you take of this medicine in one day?” Responses to the first question were independently rated as either correct or incorrect by three general internal medicine attending physicians from three different academic medical centers. Patients had to respond correctly to both questions in order to be classified as having correctly interpreted a prescription instruction. This was deemed necessary as a prior study found that patients could passively repeat instructions but not operationalize them by correctly identifying the proper dose of the medication.⁵

Blinding and Coding

The three physician raters who coded the patients' verbatim responses to the first question describing appropriate use were blinded to all patient information and trained to follow stringent coding guidelines pre-specified by the research team. Inter-rater reliability between the physicians was high (Kappa = 0.87). The 380 responses (8.4%) that received discordant ratings were sent to a three-member expert panel for further review and a final coding decision.

Analysis Plan

A generalized linear model with a Poisson distribution and complementary log link function was used to estimate the risk ratio of correct interpretation of dosage instructions for covariates in the model compared to each referent condition. Robust error estimation was used to correct for overestimation of variance resulting from using Poisson distribution for binomial outcome. The primary independent variable of interest was label type (standard, PCL, PCL + Graphic). The final multivariate model included the potential confounding variables age, gender, race (African American vs. white), literacy, education, and number of medications currently taken daily. Patient literacy was classified as low ($\leq 6^{\text{th}}$ grade), marginal (7^{th} - 8^{th} grade) or adequate ($\geq 9^{\text{th}}$ grade). Interaction terms between label type, literacy, age, and regimen complexity were included in models to determine whether associations varied according to these characteristics. Statistical analyses were performed using STATA 10.0 (College Station, TX).

Results

[Table 2](#) presents the sociodemographic characteristics of subjects. Overall, patient literacy was limited; 20.2 percent were reading below a 7^{th} grade level (low literacy) and 32.0 percent were reading at the 7^{th} - 8^{th} grade level (marginal literacy). Lower literacy was associated with older age ($p < 0.001$), African American race ($p < 0.001$), less education ($p < 0.001$), and the Shreveport study

site ($p < 0.001$). No significant differences were reported between literacy level, gender or number of prescription medications taken daily.

Variable	All Subjects (n=588)	Literacy Level	
		Low (n=181)	Marginal (n=407)
Age, Mean (SD)	48.9 (14.4)	48.3 (13.3)	49.0 (14.8)
Male, %	39.6	44.6	38.8
Race, %			
African American	63.6	90.1	63.1
White	32.8	6.9	35.0
Other	3.6	3.0	1.9
Years of Education, %			
< 12	19.4	36.6	20.0
≥ 12	80.2	63.4	80.2

Table 2
Characteristics of Study Sample, Stratified by Literacy Level

Overall rates of correct interpretation to prescription drug container label instructions varied among standard, PCL, and PCL + Graphic labels (69%, 91%, and 86% respectively, $p < 0.001$). PCL instructions (with or without graphic aid) were more likely to be correctly interpreted than their standard label counterparts when a drug was to be taken 2 times (88% and 84% vs. 77%, $p < 0.04$) or 3 times per day (91% and 91% vs. 44%, $p < 0.001$).

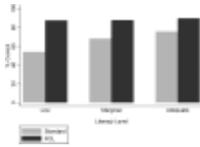
In multivariate analyses, prescription instructions with the PCL format were significantly more likely to be correctly interpreted compared to standard instructions (Adjusted Relative Risk (RR) 1.33, 95% Confidence Interval (CI) 1.25 – 1.41, $p < 0.001$; [Table 3](#)). The inclusion of the graphic aid on the label (PCL + Graphic) significantly decreased rates of correct interpretation compared to the PCL instructions alone (RR 0.93, 95% CI 0.89 - 0.97, $p = 0.001$). Greater regimen complexity, less education, and fewer prescription medications currently taken by patients all were significant independent predictors of lower rates of correct interpretation.

Variable	Correct Interpretation		
	RR	95% CI	P value
Instruction Type			
Standard			
Patient-Centered Label (PCL)	1.33	(1.25 - 1.41)	<0.001
Use of Graphic			
No graphic on label			
Graphic on label	0.93	(0.89 - 0.97)	0.001
Regimen complexity			
1 pill a day			
2 pills a day	0.85	(0.80 - 0.90)	0.02

Table 3
Generalized Estimating Equation (GEE) Model for Correct Interpretation of Prescription Label Instructions.

Low literacy was not associated with misinterpretation (RR 0.95, 95% CI 0.86 – 1.04, $p = 0.25$). However, a significant interaction between literacy and label type was found; low literate patients were more likely to correctly interpret PCL instructions compared to standard label instructions (low literacy: RR 1.39, 95% CI 1.14 – 1.68; $p = 0.001$; see [Figure](#)). Among subjects with low literacy, the graphic aid did not improve or hinder comprehension compared to the PCL instructions alone (RR 0.98, 95% CI 0.88 – 1.10; $p = 0.75$). In addition, an interaction between regimen complexity and label type was found; differences between rates of correct interpretation

for the PCL and standard instructions was significant for the most complex regimen (refer to [Table 1](#), regimen 3 - RR 2.00, 95% CI 1.44 – 2.42; $p < 0.001$). The addition of the graphic aid did not benefit interpretation by regimen.



[Figure 1](#)

Rates of correct interpretation by literacy Level and Study Arm

Discussion

Patient-centered label instructions that used explicit time periods significantly improved understanding of the appropriate time medications should be taken. Rates of understanding PCL instructions exceeded 90 percent in this diverse sample of patients. These rates were even higher than those achieved previously using clock times (8am, 5pm) or periods of day in an earlier investigation by this research team.¹⁶ The PCL format was particularly useful for patients with low literacy skills and when regimens displayed some level of complexity (i.e. > one pill a day).

The inclusion of a graphic aid to support comprehension among the elderly and those with limited literacy provided no additional benefit and may even impair comprehension. Currently there is disagreement in the literature on the use of icons, particularly among the elderly to convey medication use, and table formats have been found to be challenging among lower literate adults.²⁴⁻²⁸ It is possible the graphic aid was redundant, causing confusion as subjects tried to interpret and mentally resolve both presentations. In the second and third regimens given to patients where the prescribed drug was to be taken at multiple time periods, rates of correct interpretation were higher for the PCL + graphic compared to the standard, but not when compared to the PCL alone. This emphasizes the importance of first validating even intuitively reasonable interventions.

Contrary to prior findings, lower literacy was not associated with incorrect interpretation of prescription instructions. However, fewer years of schooling was significantly linked to poorer patient understanding. This might be explained by a more diverse sample or possibly model over-adjustment. We also found a threshold that patients currently taking ≥ 3 prescription medications were more likely to correctly interpret instructions. It could be that prior experience with a medication, and/or physicians and pharmacists, may have helped individuals comprehend instructions for these hypothetical regimens.

Our study did not examine the association between misinterpretation of prescription instructions and actual error in taking real medications. We also did not have information on patients' health background; in particular whether they had actual experience with medication use because the study design did not include a formal chart review. Patients' motivation, concentration and comprehension might have been greater if they were reporting on their own medicine given by their physician for conditions they actually had.²⁹⁻³² Although patients were not randomly assigned, no differences were noted by demographic characteristics across study arms. Finally,

the generalizability of our findings may be limited as patients were predominantly African American and female, and that participation was limited to patients who spoke English.

Further enhancements to the PCL instructions may be required. For example, attention must be given to tailoring directions for patients who work at night, or who fast for long periods of the day for cultural reasons. Also strategies must be developed to address instructions for prescription drugs that are to be taken only as needed, for non-pill form medications, medications with tapered doses, and for complex regimens that include auxiliary warnings and precautions that would affect how a patient administers a drug (i.e. with food, not to lie down after taking). We are currently learning more about the feasibility and effectiveness of the PCL to improve patients' actual use of prescription medications within a clinical trial funded by the Agency for Healthcare Research and Quality.^{33,34} There are also clear opportunities for the PCL approach to become a standard, as it was included in recent legislation passed by the State Board of Pharmacy in California to promote better labeling practices.³⁵

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Footnotes

Statement of Conflict of Interest: None of the authors have conflicts to disclose with regard to the work presented in this manuscript.

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Helping patients simplify and safely use complex prescription regimens.

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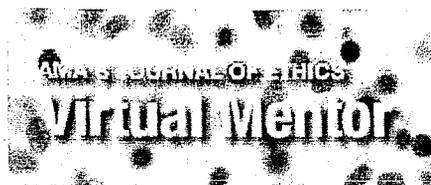
Abstract

BACKGROUND: There is considerable variability in the manner in which prescriptions are written by physicians and transcribed by pharmacists, resulting in patient misunderstanding of label instructions. A universal medication schedule was recently proposed for standardizing prescribing practices to 4 daily time intervals, thereby helping patients simplify and safely use complex prescription regimens. We investigated whether patients consolidate their medications or whether there is evidence of unnecessary regimen complexity that would support standardization.

METHODS: Structured interviews were conducted with 464 adults (age range, 55-74 years) who were receiving care either at an academic general medicine practice or at 1 of 3 federally qualified health centers in Chicago, Illinois. Participants were given a hypothetical, 7-drug medication regimen and asked to demonstrate how and when they would take all of the medications in a 24-hour period. The regimen could be consolidated into 4 dosing episodes per day. The primary outcome was the number of times per day that individuals would take medication. Root causes for patients complicating the regimen (>4 times a day) were examined.

RESULTS: Participants on average identified 6 times (SD, 1.8 times; range, 3-14 times) in 24 hours to take the 7 drugs. One-third of the participants (29.3%) dosed their medications 7 or more times per day, while only 14.9% organized the regimen into 4 or fewer times a day. In multivariable analysis, low literacy was an independent predictor of more times per day for dosing the regimen ($\beta = 0.67$; 95% confidence interval, 0.12-1.22; $P = .02$). Instructions for 2 of the drugs were identical, yet 31.0% of the participants did not take these medications at the same time. Another set of drugs had similar instructions, with the primary exception of 1 drug having the added instruction to take "with food and water." Half of the participants (49.5%) took these medications at different times. When the medications had variable expressions of the same dose frequency (eg, "every 12 hours" vs "twice daily"), 79.0% of the participants did not consolidate the medications.

CONCLUSIONS: Many patients, especially those with limited literacy, do not consolidate prescription regimens in the most efficient manner, which could impede adherence. Standardized instructions proposed with the universal medication schedule and other task-centered strategies could potentially help patients routinely organize and take medication regimens.



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Original Investigation | February 28, 2011

HEALTH CARE REFORM

Helping Patients Simplify and Safely Use Complex Prescription Regimens FREE

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ABSTRACT

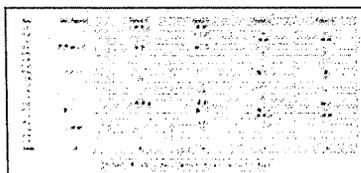
[ABSTRACT](#) | [METHODS](#) | [RESULTS](#) | [COMMENT](#) | [ARTICLE INFORMATION](#) | [REFERENCES](#)

Background There is considerable variability in the manner in which prescriptions are written by physicians and transcribed by pharmacists, resulting in patient misunderstanding of label instructions. A universal medication schedule was recently proposed for standardizing prescribing practices to 4 daily time intervals, thereby helping patients simplify and safely use complex prescription regimens. We investigated whether patients consolidate their medications or whether there is evidence of unnecessary regimen complexity that would support standardization.

Methods Structured interviews were conducted with 464 adults (age range, 55-74 years) who were receiving care either at an academic general medicine practice or at 1 of 3 federally qualified health centers in Chicago, Illinois. Participants were given a hypothetical, 7-drug medication regimen and asked to demonstrate how and when they would take all of the medications in a 24-hour period. The regimen could be consolidated into 4 dosing episodes per day. The primary outcome was the number of times per day that individuals would take medication. Root causes for patients complicating the regimen (>4 times a day) were examined.

Results Participants on average identified 6 times (SD, 1.8 times; range, 3-14 times) in 24 hours to take the 7 drugs. One-third of the participants (29.3%) dosed their medications 7 or more times per day, while only 14.9% organized the regimen into 4 or fewer times a day. In multivariable analysis, low literacy was an independent predictor of more times per day for dosing the regimen ($\beta = 0.67$; 95% confidence interval, 0.12-1.22; $P = .02$). Instructions for 2 of the drugs were identical, yet 31.0% of the participants did not take these medications at the same time. Another set of drugs had similar instructions, with the primary exception of 1 drug having the added instruction to take "with food and water." Half of the participants (49.5%) took these medications at different times. When the medications had variable expressions of the same dose frequency (eg, "every 12 hours" vs "twice daily"), 79.0% of the participants did not consolidate the medications.

Conclusions Many patients, especially those with limited literacy, do not consolidate prescription regimens in the most efficient manner, which could impede adherence. Standardized instructions proposed with the universal medication schedule and other task-centered strategies could potentially help patients routinely organize and take medication regimens.



Figures in this Article

Patients frequently misunderstand common instructions and warnings that accompany prescription drugs, resulting in unintentional misuse and potentially adverse drug events.¹⁻⁶ This should not be surprising, as prescription labels may provide seemingly simple but often unclear directions that are confusing to most patients. In the United States, physician prescriptions and pharmacy labeling typically include vague information detailing recommended medication schedules described either in hourly intervals (eg, every 4-6 hours) or times per day (eg, twice daily). Davis et al¹ found that nearly half of patients misinterpreted common instructions when attempting to dose a single prescription medication.

Yet the problem may be more serious than these findings suggest, as patients are increasingly managing multiple prescriptions and over-the-counter medications. According to the Medical Expenditure Panel Survey, the average adult in the United States fills 9 prescriptions annually,⁷ while adults older than 65 years fill on average 20 prescriptions a year. Greater regimen complexity, based on multiple medications and/or multiple daily doses per drug, may lead to poorer adherence, which in turn will lead to worse health outcomes.⁸⁻¹² From a health system perspective, the known variability and poor quality in the manner in which prescription instructions are written by physicians and translated by pharmacies impede an individual's ability to organize and properly dose multiple medications.¹³⁻¹⁴

The Institute of Medicine, in its 2008 report *Standardizing Medication Labels*, recognized the need for setting standards within prescribing and dispensing practices to promote safe and accurate medication use for patients.⁶ Because approximately 90% of prescriptions are taken 4 or fewer times a day,¹² a universal medication schedule (UMS) was proposed in the Institute of Medicine report specifying 4 standard times (morning, noon, evening, and bedtime) for the prescribing and dispensing of medication.¹⁴ The UMS would describe when to take a drug in the same manner on all prescription labels, removing the current variability often found in the manner in which prescriptions are written by physicians and transcribed by pharmacists.¹³⁻¹⁵ All prescriptions would instruct patients to take their medications using these specified times, and label instructions would subsequently be described in a single standardized fashion. This standardization was viewed with both promise and controversy by the pharmacological and medical communities. While it might help patients organize and group increasingly complex medication regimens for daily use, it was concluded that further evidence would be needed to support the need for the UMS. In the present study, we sought to fill the gap of existing literature and to investigate whether patients complicate multiple prescription regimens by taking medications more than 4 times a day. Specifically, we evaluated the accuracy and variability in the way patients implemented a typical 7-drug regimen.

METHODS

ABSTRACT | METHODS | RESULTS | COMMENT | ARTICLE INFORMATION |
REFERENCES

PARTICIPANTS

Adults between the ages of 55 and 74 years who received care either at an academic general internal medicine ambulatory care clinic or at 1 of 3 federally qualified health centers in Chicago, Illinois, were recruited for a National Institute of Aging study, referred to as *LitCog*, that examined performance on everyday health tasks, including medication use. Patient enrollment took place between August 2008 and December 2009. Patients were ineligible if they had severe visual or hearing impairments, were too ill to participate, or were non-English speaking. The institutional review board of Northwestern University approved the study, and all patients gave informed consent before participation. A total of 2168 patients were identified through electronic health record systems at clinic sites as initially eligible to participate in *LitCog* by age. A random sample of 1012 eligible patients were selected to be contacted by research staff via telephone and invited to participate in the study. Of those contacted, 479 refused to participate, 12 were deceased, and 521 ultimately consented to participate. Initial screening deemed 57 participants as ineligible because of severe cognitive or hearing impairment ($n = 22$), limited English-language proficiency ($n = 11$), or not being connected to a clinic physician (defined as ≥ 2 visits in the past 2 years [$n = 24$]). In all, 464

patients participated in the study, for a determined response rate of 52.1%, following American Association for Public Opinion Research guidelines.¹⁶

DATA AND PROCEDURE

Participants completed a 2-hour, structured cognitive interview that included an assessment of their ability to perform everyday health tasks, including dosing a 7-drug medication regimen over the course of a 24-hour period. A research assistant gave patients a hypothetical drug regimen, which consisted of 7 actual prescription drug pill bottles with mock-up labels, each with a retired drug name and different dosing instruction (Table 1). The drug names that were chosen were specifically used to avoid the influence of participants' potential current or prior experience with an actual drug.

Table 1. Drug Names and Instructions

Drug Name	Instructions
1. [Illegible]	[Illegible]
2. [Illegible]	[Illegible]
3. [Illegible]	[Illegible]
4. [Illegible]	[Illegible]
5. [Illegible]	[Illegible]
6. [Illegible]	[Illegible]
7. [Illegible]	[Illegible]

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The task presented to participants was to demonstrate when they would take the entire regimen by dosing fake pills contained with each prescription bottle at the times of day that they would take the drug. The research assistant gave patients a medication box, which had 24 slots labeled with every hour of the day (12 AM-11 PM), and instructed them to place the correct number of pills in the slots that identified the times when they would take a medicine. Unlike a pill organizer, the medication box was not meant to assist participants. Instead, it allowed them to demonstrate precisely at what times during the course of a day they would take each drug. The scripted verbal instruction given to patients was, "Imagine that your doctor has prescribed you these medicines. I would like you to please show me when you would take these medicines over the course of 1 day." Detailed guidance was then provided to patients on how to demonstrate, with the fake pills, how to dose the regimen using the medication box.

In addition to completing this task, patients answered basic demographic questions and completed a literacy assessment known as the Newest Vital Sign.¹⁷ This is a 6-item measure that includes reading comprehension and numeracy items based on a nutritional facts label. The Newest Vital Sign is strongly correlated with the Short Test of Functional Health Literacy in Adults.¹⁸

OUTCOME AND ANALYSIS PLAN

The outcome of interest was the number of times per day that patients would propose to take the medicine, based on the manner in which they dosed the 7-drug regimen throughout a 24-hour period as demonstrated using the medication box. Descriptive statistics were calculated for each variable. The association between participant sociodemographic characteristics and the number of reported times per day that patients would take the 7-drug regimen were evaluated with *t* tests. Multivariable linear regression analyses were then conducted to examine patient characteristics that independently predicted taking medication at more times throughout a single day. Only variables that were found to be associated with the outcome with a set value of $P < .20$ were included in the multivariable model. All statistical analyses were performed using Stata version 10 (Stata Corp, College Station, Texas).

RESULTS

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The mean (SD) age of the participants was 63.3 (5.3) years; most (71.1%) were female, white (60.8%), and highly educated (61.4% college graduates), with a household income greater than \$50 000 (61.9%). Nearly half of the participants, however, were identified as having either low (20.7%) or marginal (22.8%) health literacy skills. Eighty-four percent of the participants reported having 1 or more chronic health conditions (Table 2).

Table 2. Mean Number of Doses Identified in a 24-Hour Period, Stratified by Patient Characteristics

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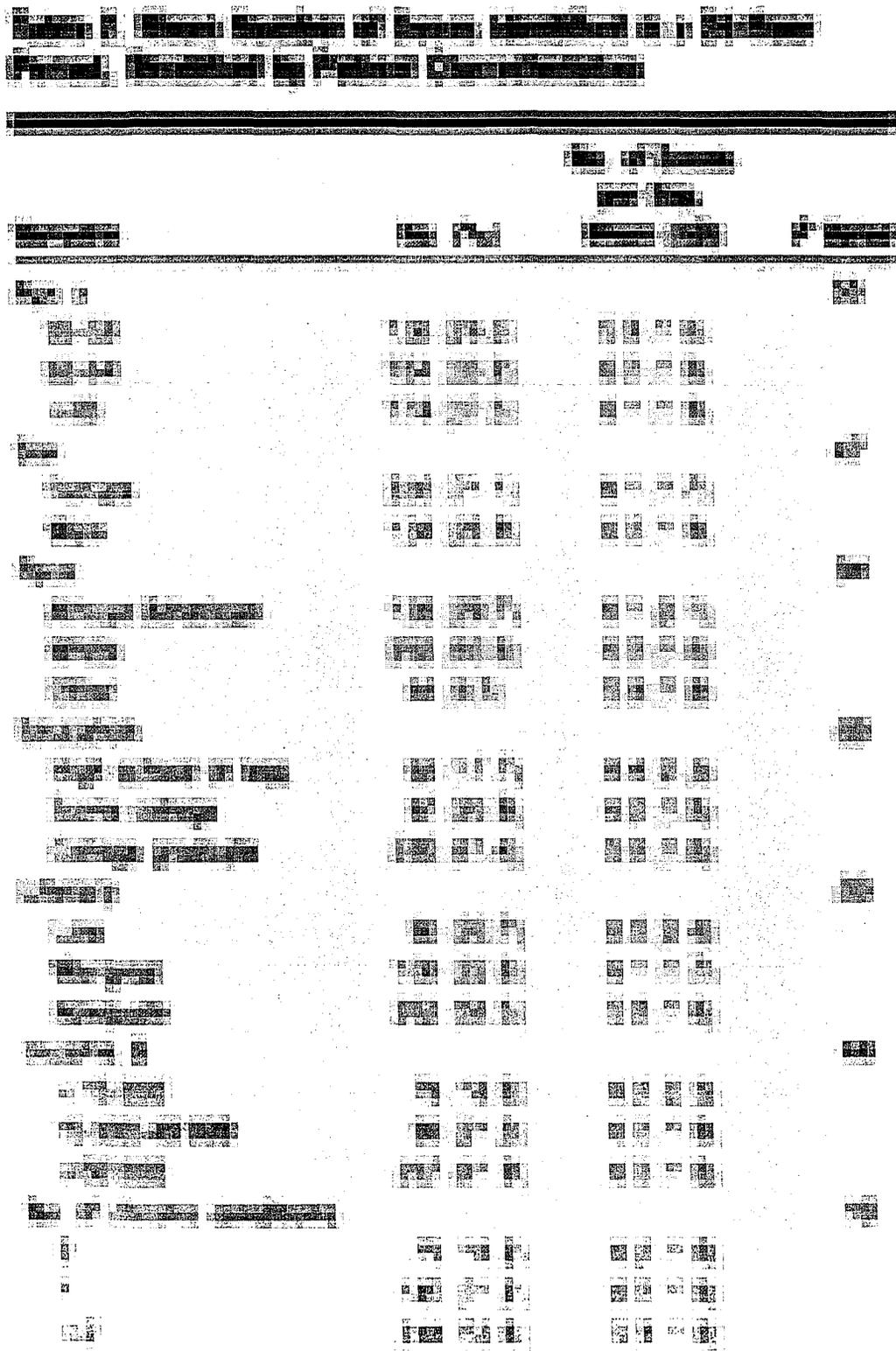
When dosing the 7-drug regimen, participants on average identified 6 times (SD, 1.8 times) in 24 hours to take medicine. Regimen dosing ranged from as few as 3 to as many as 14 times a day. Approximately one-third of the participants (29.3%) dosed the regimen 7 or more times within 24 hours, while only 14.9% organized the medication 4 or fewer times a day, as would be suggested through the proposed universal medication schedule. Examples of how patients actually dosed the regimen is shown in the Figure.

Figure.

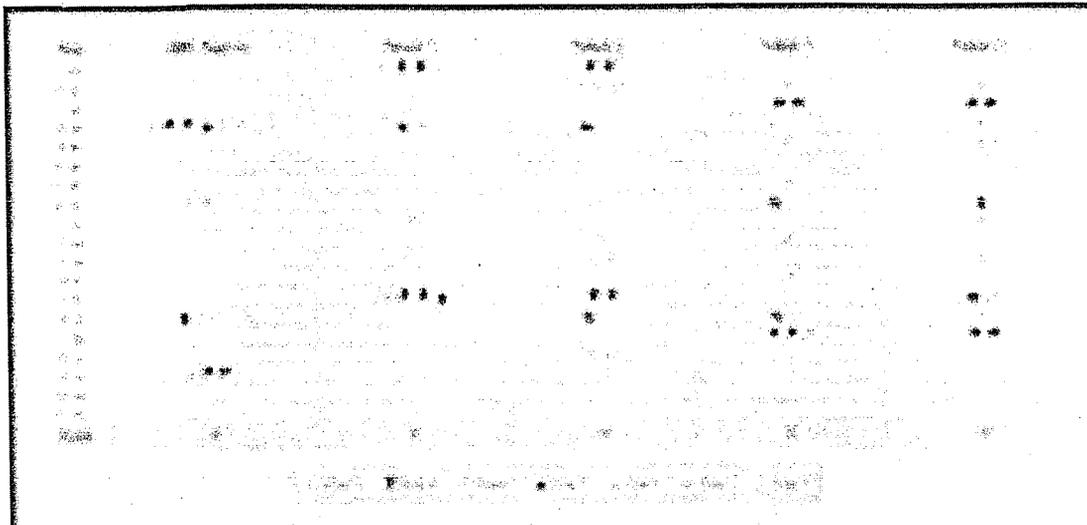
Case examples of older adults' dosing of a 7-drug regimen. UMS indicates universal medication schedule.

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In



multivariable analysis that included the covariates of education, health literacy, and number of self-reported chronic conditions, low health literacy was found to be the sole independent predictor of a greater number of times per day for dosing the 7-drug regimen ($\beta = 0.67$; 95% confidence interval, 0.12-1.22; $P = .02$). Interactions between all patient characteristics were examined. Patients with low health literacy and no



chronic conditions on average dosed the regimen the most times daily compared with others (8.4 times a day vs range of 5.6 to 6.3 times per day

among other groups by literacy and chronic conditions, $P = .005$). No other interactions by age, race, education, literacy, or chronic conditions were statistically significant.

To identify explanations for participants' failure to consolidate the medications into 4 or fewer times per day, we examined in detail how they handled 3 specific sets of drugs within the hypothetical regimen that could have been taken at the same time. Suspected root causes linked to each set were (1) overall difficulty taking multiple medications and coordinating doses (set 1); (2) distraction of secondary, or auxiliary, instructions (set 2); and (3) variability in language used to identify the interval between doses (set 3). In the first set, the dosage instructions were exactly the same (drugs E and F, Table 1). Nearly one-third of the participants (30.8%) did not take these drugs at the same hours of the day despite having identical label instructions.

In the second set, we investigated 2 drugs (F and G) that could also be taken at the same daily intervals (3 times daily), yet 1 drug included the additional instruction to be taken "with food and water." Half of the participants (49.5%) did not take these medications at the same time of day. In the final set, medications that were to be taken 2 times a day (drugs A and B) were compared; drug A expressed frequency as "twice daily," while drug B stated that it was to be taken "every 12 hours." Four of 5 patients (79.0%) did not consolidate these variable expressions of dose frequency and took the 2 drugs at different times. Notably, drug A instructions also included an auxiliary comment that the medication should be taken for 10 days, and in both the second and third sets investigated, the dose (1 or 2 tablets) also varied.

Beyond examination of the drug set scenarios described herein, Table 3 details how long the participants demonstrated that they would wait between doses for medications that were to be taken 2 (drugs A, B, and D) and 3 (drugs E, F, and G) times a day. Considerable variability was found among participants with regard to how many hours they would allot between doses for both 2- and 3-times-a-day regimens. For drugs to be taken twice daily, participants averaged 10.3 hours (SD, 3.0 hours) between doses, with as few as 1 and as many as 18 hourly intervals (interquartile range, 0-12 hourly intervals). For regimens of 3 times a day, the hourly intervals ranged from 1 to 13 hours, with the mean (SD) being 5.4 (1.8) hours between the first and second dose (interquartile range, 4-7 hours) and 6.5 (1.5) hours between the second and third doses (interquartile range, 6-8 hours).

Table 3. Older Adults' Dosing of Medications to Be Taken 2 or 3 Times a Day

Table 1. Older Adults' Grouping and Medication Regimens by the Number of Times a Day

Medication Regimen	Number of Times a Day	Number of Patients	Percentage of Patients
1 medication	1	10	10.0%
1 medication	2	10	10.0%
1 medication	3	10	10.0%
1 medication	4	10	10.0%
1 medication	5	10	10.0%
1 medication	6	10	10.0%
1 medication	7	10	10.0%
1 medication	8	10	10.0%
1 medication	9	10	10.0%
1 medication	10	10	10.0%
2 medications	1	10	10.0%
2 medications	2	10	10.0%
2 medications	3	10	10.0%
2 medications	4	10	10.0%
2 medications	5	10	10.0%
2 medications	6	10	10.0%
2 medications	7	10	10.0%
2 medications	8	10	10.0%
2 medications	9	10	10.0%
2 medications	10	10	10.0%
3 medications	1	10	10.0%
3 medications	2	10	10.0%
3 medications	3	10	10.0%
3 medications	4	10	10.0%
3 medications	5	10	10.0%
3 medications	6	10	10.0%
3 medications	7	10	10.0%
3 medications	8	10	10.0%
3 medications	9	10	10.0%
3 medications	10	10	10.0%

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COMMENT

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Our findings demonstrate that most patients may self-administer multidrug regimens more times a day than necessary and that those with limited literacy are at greater risk. This increased complexity, at the very least, translates to taking medication too often each day, leading to substantial interference with patients' lives. As a result, doses may be frequently missed or incorrectly administered. Given the heightened concerns of medication safety and adherence, particularly among the elderly, who take more medicine and are increasingly cognitively challenged,¹⁹ we offer evidence that previously was unavailable. In particular, strategies are needed to help patients not only to understand how to take a particular medicine but also to consolidate and simplify how to take an entire drug regimen.

The inherent complexity of the task of organizing multiple medications into as few times per day may be an apparent reason that so many patients do not use more efficient consolidation strategies. This is evident in our finding that 1 in 3 older adults did not take 2 medications (drugs E and F) that had the exact same dosage instruction at the same time. Variability in how prescriptions are written, both in describing the timing of doses and the expression of auxiliary instructions, further distracts individuals from the goal of consolidating regimens. Yet many patients may not explicitly perceive finding the most efficient medication-taking strategy to be the objective. It is also possible that patients might not understand that they can take different medications at the same time, especially when the instructions are not identical.

Our study has certain limitations. First, we investigated older adults' dosing of a hypothetical medication regimen and not their actual medication. Therefore, the context and task of demonstrating use via the medication box might not directly reflect the way that participants would self-administer prescribed drugs

in their daily life. Further research is needed to investigate in-depth patient dosing strategies and beliefs about their own regimens. Second, our study was limited to the outcome of demonstration of medication use for a multidrug regimen, and not adherence. While prior studies support the premise that taking medication more times daily could negatively affect long-term regimen adherence, our findings do not directly offer evidence for that association. Third, our analysis of root causes of overcomplicating regimens was post hoc and exploratory, and other aspects of the instruction for sets 2 and 3, such as different doses (1 vs 2 tablets), could have contributed to patient confusion. Fourth, our sample was representative of older adults of higher socioeconomic strata, as indicated by education attainment and household income. However, our findings should be viewed as the best case scenario, as more socioeconomically disadvantaged patients are more likely to have limited health literacy and face even greater difficulty in organizing and dosing complex medication regimens.²⁰⁻²¹ Finally, we provided participants only with the task of demonstrating how and when they would take a 7-drug regimen; a large proportion of chronically ill and elderly patients take far more medications daily. Therefore, our findings may provide a conservative estimate of the potential confusion older adults face when attempting to consolidate and manage all of their prescribed medications.

The UMS was not directly evaluated, but our study highlights patient confusion surrounding medication use. Standardized instructions could be one of many remedies to aid patients and families. Of note, an efficacy trial of the UMS to improve patient comprehension was also conducted recently; findings show that patients are better able to dose medications safely with UMS vs current standard instructions.²² With these findings and the Institute of Medicine report, legislation has already been approved and passed by the State Board of Pharmacy in California requiring pharmacies to use these UMS instructions when applicable.²³ Further study of the possible benefits, as well as risks, of the UMS strategy is warranted, and evidence will soon be available from ongoing National Institutes of Health and Agency for Healthcare Research and Quality (AHRQ) studies that are currently testing the UMS in actual use (AHRQ grants R01 HS017687 and R01 HS019435).²⁴

If standardizing prescription instructions does aid patients in consolidating and taking their medication regimens, the UMS could further unite medical and pharmacological practice. Beyond pharmacy labeling, physicians could write the instructions with the more explicit UMS times to help patients have an adequate understanding of when to take not only their newly prescribed medications but also their entire regimen at the point of prescribing. Opportunities now exist with medical practices increasingly adopting electronic health record systems to leverage these tools and to standardize prescribing practices following the UMS concept (National Institutes of Health grant R21 CA132771 and AHRQ grant R18 HS017220). By working across the medication prescribing and dispensing continuum, the previously noted variability within and between physician prescription writing and pharmacist transcribing can be reduced, and patient understanding and adherence to medication regimens can be improved.¹⁴⁻¹⁶

We offer compelling, preliminary evidence of the need to help all patients more clearly understand, organize, and simplify their medication regimens. While providing standard, explicit instructions is one possible response, other interventions will likely be necessary. For instance, drug labeling is meant to support, not replace, prescriber and pharmacist spoken communication with patients. Educational and health system strategies are needed to target provider communication skills and screening methods for identifying those at risk for complicating regimens and poor adherence. Similarly, prescribing 1-a-day regimens and bundling medications by times per day at the pharmacy might also be possible solutions.

Ultimately, public health initiatives should help patients acquire a fundamental understanding of prescription medication use and when it would be safe and appropriate to take medications together.

ARTICLE INFORMATION

ABSTRACT | METHODS | RESULTS | COMMENT | ARTICLE INFORMATION |
REFERENCES

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Author Contributions: *Study concept and design:* Wolf, Davis, Parker, and Wood. *Acquisition of data:* Wolf and Waite. *Analysis and interpretation of data:* Wolf, Curtis, Bailey, Hedlund, Davis, Shrank, Parker, and Wood. *Drafting of the manuscript:* Wolf, Davis, and Wood. *Critical revision of the manuscript for important intellectual content:* Wolf, Curtis, Waite, Bailey, Hedlund, Davis, Shrank, Parker, and Wood. *Statistical analysis:* Wolf, Curtis, and Shrank. *Obtained funding:* Wolf and Davis. *Administrative, technical, and material support:* Wolf, Waite, Bailey, and Hedlund. *Study supervision:* Shrank.

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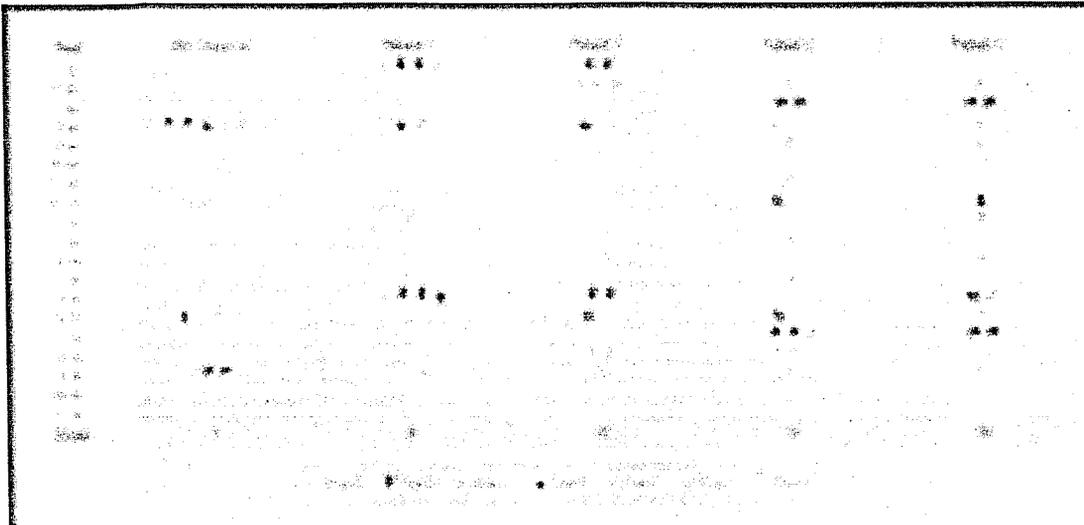
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Figures

Figure.

Case examples of older adults' dosing of a 7-drug regimen. UMS indicates universal medication schedule.



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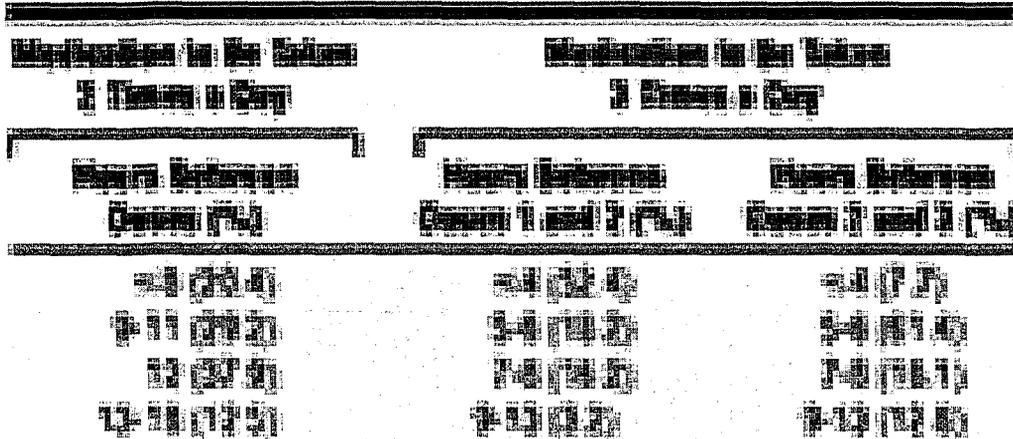
Table 1. Drug Names and Instructions

Drug Name	Instruction
Drug 1	Instruction 1
Drug 2	Instruction 2
Drug 3	Instruction 3
Drug 4	Instruction 4
Drug 5	Instruction 5
Drug 6	Instruction 6
Drug 7	Instruction 7

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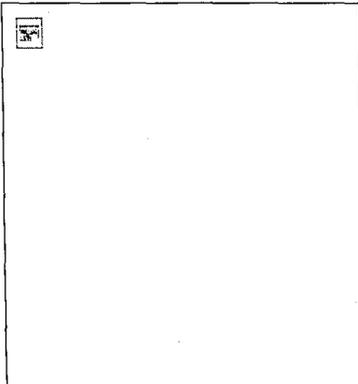
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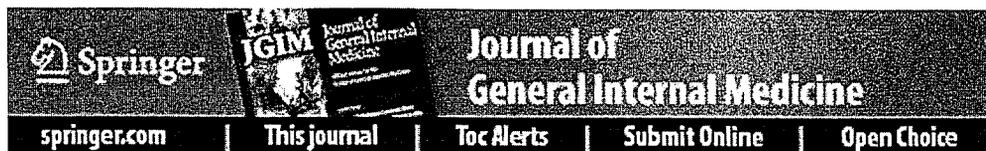
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Improving Patient Understanding of Prescription Drug Label Instructions

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Abstract

Background

Patient misunderstanding of instructions on prescription drug labels is common and a likely cause of medication error and less effective treatment.

Objective

To test whether the use of more explicit language to describe dose and frequency of use for prescriptions could improve comprehension, especially among patients with limited literacy.

Design

Cross-sectional study using in-person, structured interviews.

Patients

Three hundred and fifty-nine adults waiting for an appointment in two hospital-based primary care settings: one federally qualified health center in Shreveport, Louisiana; Chicago, Illinois; and New York, New York, respectively.

Measurement

Correct understanding of each of ten label instructions as determined by a blinded panel review of patient verbatim responses.

Results

Patient understanding of prescription label instructions ranged from 53% for the least understood to 93% for the most commonly understood label. Patients were significantly more likely to understand instructions with explicit times periods (i.e., morning) or precise times of day compared to instructions stating times :

(i.e., twice) or hourly intervals (89%, 77%, 61%, and 53%, respectively, < 0.001). In multivariate analysis, dosage instructions with specific times or time periods were significantly more likely to be understood compared to instructions stating times per day (time periods — adjusted relative risk ratio (ARR) 0.34, 95% Confidence Interval (CI) 0.34–0.52; specific times — ARR 0.60, 95% CI 0.49–0.74). Low and marginal literacy remained statistically significant independent predictors of misinterpreting instructions (low - ARR 1.81–4.03; marginal - ARR 1.66, 95% CI 1.18–2.32).

Conclusions

Use of precise wording on prescription drug label instructions can improve patient comprehension. Patients with limited literacy were more likely to misinterpret instructions despite use of more explicit language.

Key Words: literacy, health literacy, drugs, prescription medications, labels, patient safety, medication regimens

Patient misunderstanding of instructions on prescription drug labels is a medication safety and health concern^{1–3}. The 2006 Institute of Medicine Report, *Preventing Medication Errors*, cited poor patient comprehension and subsequent unintentional misuse of prescription drugs as a root cause of medication non-adherence, and worse health outcomes³. A recent study by our research team found nearly half of low literacy care patients misunderstood common dosage instructions on prescription container labels⁴. Patient limited literacy and those taking more medications were at greatest risk. As patients, particularly those taking an increasing number of prescription drugs, the ability to accurately interpret medication instructions becomes even more critical for ensuring proper and safe use^{5,6}.

While limited literacy may impede patient comprehension of medication dosage instructions, the instructions also may not be written in the most clear and precise manner^{7–10}. There is little evidence supporting best practices for writing prescription medication dosage instructions to promote patients' understanding. Data from our previous study and earlier cognitive factors research suggest that less complex and more explicit dosage instructions might improve patient understanding^{4,7,11–15}. The purpose of this study was to evaluate whether the use of more explicit language to describe the dose and frequency of prescribed drugs could improve comprehension, especially among patients with limited literacy. We hypothesized that more explicit instructions would improve patient interpretation, and the association between literacy and understanding how to take prescribed drugs would be reduced.

METHODS

Subjects

Study participants were adult patients who attended one of three outpatient primary care clinics in Louisiana, Chicago, Illinois and New York, New York. All of these study clinics provide care for a large number of indigent patients. Subject recruitment took place from May to December 2006. The Shreveport and New York clinics were within a public university hospital while the Chicago study clinic was a Federally C

Health Center. Institutional Review Boards at the affiliated institutions (Louisiana State University Sciences Center at Shreveport, Northwestern University, Mount Sinai School of Medicine) approved. Patients at the three clinics were eligible if they were 18 years of age or older. Research assistants (RA) approached consecutive patients in each clinic while they were waiting to see physicians. Patients were excluded from participation if they reported they had severely impaired vision, hearing problems, were ill, or did not speak English. A total of 401 patients were approached and 373 consented to the study. Individuals were excluded based on language barriers, and three were ineligible due to visual impairment. All, 359 consented to the study (90% response rate).

Selection of Prescription Instructions

We studied instruction labels for three commonly prescribed medications: glyburide, metformin, and atenolol. Three physicians and one pharmacist identified a typical dose for each medication, along with various frequencies of use for the drug's daily administration. Atenolol was written to be taken once a day, while glyburide and metformin were written for twice a day. A minimum of three variations of the dosage instructions were used per drug, ranging from vague to most explicit. Specifically, frequency of use for a prescribed drug was presented either as 1) number of times per day ("twice daily"), 2) hourly intervals ("every 12 hours"), 3) time periods ("morning", "evening"), or 4) specific times ("8 A.M.", "5 P.M."; Table 2). Ten mock pill bottles were developed based on these different presentations of dose (number of pills and frequency of use (number of times to be taken per day) for the three drugs.

Instruction	Correct Interpretation	Incorrect Interpretation
Twice daily	2	2
Every 12 hours	2	2
Twice a day	2	2
Twice a week	2	2
Twice a month	2	2
Twice a year	2	2
Twice a lifetime	2	2
Twice a day, every 12 hours	2	2
Twice a day, every 24 hours	2	2
Twice a day, every 36 hours	2	2
Twice a day, every 48 hours	2	2
Twice a day, every 60 hours	2	2
Twice a day, every 72 hours	2	2
Twice a day, every 84 hours	2	2
Twice a day, every 96 hours	2	2
Twice a day, every 108 hours	2	2
Twice a day, every 120 hours	2	2
Twice a day, every 132 hours	2	2
Twice a day, every 144 hours	2	2
Twice a day, every 156 hours	2	2
Twice a day, every 168 hours	2	2
Twice a day, every 180 hours	2	2
Twice a day, every 192 hours	2	2
Twice a day, every 204 hours	2	2
Twice a day, every 216 hours	2	2
Twice a day, every 228 hours	2	2
Twice a day, every 240 hours	2	2
Twice a day, every 252 hours	2	2
Twice a day, every 264 hours	2	2
Twice a day, every 276 hours	2	2
Twice a day, every 288 hours	2	2
Twice a day, every 300 hours	2	2
Twice a day, every 312 hours	2	2
Twice a day, every 324 hours	2	2
Twice a day, every 336 hours	2	2
Twice a day, every 348 hours	2	2
Twice a day, every 360 hours	2	2
Twice a day, every 372 hours	2	2
Twice a day, every 384 hours	2	2
Twice a day, every 396 hours	2	2
Twice a day, every 408 hours	2	2
Twice a day, every 420 hours	2	2
Twice a day, every 432 hours	2	2
Twice a day, every 444 hours	2	2
Twice a day, every 456 hours	2	2
Twice a day, every 468 hours	2	2
Twice a day, every 480 hours	2	2
Twice a day, every 492 hours	2	2
Twice a day, every 504 hours	2	2
Twice a day, every 516 hours	2	2
Twice a day, every 528 hours	2	2
Twice a day, every 540 hours	2	2
Twice a day, every 552 hours	2	2
Twice a day, every 564 hours	2	2
Twice a day, every 576 hours	2	2
Twice a day, every 588 hours	2	2
Twice a day, every 600 hours	2	2
Twice a day, every 612 hours	2	2
Twice a day, every 624 hours	2	2
Twice a day, every 636 hours	2	2
Twice a day, every 648 hours	2	2
Twice a day, every 660 hours	2	2
Twice a day, every 672 hours	2	2
Twice a day, every 684 hours	2	2
Twice a day, every 696 hours	2	2
Twice a day, every 708 hours	2	2
Twice a day, every 720 hours	2	2
Twice a day, every 732 hours	2	2
Twice a day, every 744 hours	2	2
Twice a day, every 756 hours	2	2
Twice a day, every 768 hours	2	2
Twice a day, every 780 hours	2	2
Twice a day, every 792 hours	2	2
Twice a day, every 804 hours	2	2
Twice a day, every 816 hours	2	2
Twice a day, every 828 hours	2	2
Twice a day, every 840 hours	2	2
Twice a day, every 852 hours	2	2
Twice a day, every 864 hours	2	2
Twice a day, every 876 hours	2	2
Twice a day, every 888 hours	2	2
Twice a day, every 900 hours	2	2
Twice a day, every 912 hours	2	2
Twice a day, every 924 hours	2	2
Twice a day, every 936 hours	2	2
Twice a day, every 948 hours	2	2
Twice a day, every 960 hours	2	2
Twice a day, every 972 hours	2	2
Twice a day, every 984 hours	2	2
Twice a day, every 996 hours	2	2
Twice a day, every 1008 hours	2	2
Twice a day, every 1020 hours	2	2
Twice a day, every 1032 hours	2	2
Twice a day, every 1044 hours	2	2
Twice a day, every 1056 hours	2	2
Twice a day, every 1068 hours	2	2
Twice a day, every 1080 hours	2	2
Twice a day, every 1092 hours	2	2
Twice a day, every 1104 hours	2	2
Twice a day, every 1116 hours	2	2
Twice a day, every 1128 hours	2	2
Twice a day, every 1140 hours	2	2
Twice a day, every 1152 hours	2	2
Twice a day, every 1164 hours	2	2
Twice a day, every 1176 hours	2	2
Twice a day, every 1188 hours	2	2
Twice a day, every 1200 hours	2	2
Twice a day, every 1212 hours	2	2
Twice a day, every 1224 hours	2	2
Twice a day, every 1236 hours	2	2
Twice a day, every 1248 hours	2	2
Twice a day, every 1260 hours	2	2
Twice a day, every 1272 hours	2	2
Twice a day, every 1284 hours	2	2
Twice a day, every 1296 hours	2	2
Twice a day, every 1308 hours	2	2
Twice a day, every 1320 hours	2	2
Twice a day, every 1332 hours	2	2
Twice a day, every 1344 hours	2	2
Twice a day, every 1356 hours	2	2
Twice a day, every 1368 hours	2	2
Twice a day, every 1380 hours	2	2
Twice a day, every 1392 hours	2	2
Twice a day, every 1404 hours	2	2
Twice a day, every 1416 hours	2	2
Twice a day, every 1428 hours	2	2
Twice a day, every 1440 hours	2	2
Twice a day, every 1452 hours	2	2
Twice a day, every 1464 hours	2	2
Twice a day, every 1476 hours	2	2
Twice a day, every 1488 hours	2	2
Twice a day, every 1500 hours	2	2
Twice a day, every 1512 hours	2	2
Twice a day, every 1524 hours	2	2
Twice a day, every 1536 hours	2	2
Twice a day, every 1548 hours	2	2
Twice a day, every 1560 hours	2	2
Twice a day, every 1572 hours	2	2
Twice a day, every 1584 hours	2	2
Twice a day, every 1596 hours	2	2
Twice a day, every 1608 hours	2	2
Twice a day, every 1620 hours	2	2
Twice a day, every 1632 hours	2	2
Twice a day, every 1644 hours	2	2
Twice a day, every 1656 hours	2	2
Twice a day, every 1668 hours	2	2
Twice a day, every 1680 hours	2	2
Twice a day, every 1692 hours	2	2
Twice a day, every 1704 hours	2	2
Twice a day, every 1716 hours	2	2
Twice a day, every 1728 hours	2	2
Twice a day, every 1740 hours	2	2
Twice a day, every 1752 hours	2	2
Twice a day, every 1764 hours	2	2
Twice a day, every 1776 hours	2	2
Twice a day, every 1788 hours	2	2
Twice a day, every 1800 hours	2	2
Twice a day, every 1812 hours	2	2
Twice a day, every 1824 hours	2	2
Twice a day, every 1836 hours	2	2
Twice a day, every 1848 hours	2	2
Twice a day, every 1860 hours	2	2
Twice a day, every 1872 hours	2	2
Twice a day, every 1884 hours	2	2
Twice a day, every 1896 hours	2	2
Twice a day, every 1908 hours	2	2
Twice a day, every 1920 hours	2	2
Twice a day, every 1932 hours	2	2
Twice a day, every 1944 hours	2	2
Twice a day, every 1956 hours	2	2
Twice a day, every 1968 hours	2	2
Twice a day, every 1980 hours	2	2
Twice a day, every 1992 hours	2	2
Twice a day, every 2004 hours	2	2
Twice a day, every 2016 hours	2	2
Twice a day, every 2028 hours	2	2
Twice a day, every 2040 hours	2	2
Twice a day, every 2052 hours	2	2
Twice a day, every 2064 hours	2	2
Twice a day, every 2076 hours	2	2
Twice a day, every 2088 hours	2	2
Twice a day, every 2100 hours	2	2
Twice a day, every 2112 hours	2	2
Twice a day, every 2124 hours	2	2
Twice a day, every 2136 hours	2	2
Twice a day, every 2148 hours	2	2
Twice a day, every 2160 hours	2	2
Twice a day, every 2172 hours	2	2
Twice a day, every 2184 hours	2	2
Twice a day, every 2196 hours	2	2
Twice a day, every 2208 hours	2	2
Twice a day, every 2220 hours	2	2
Twice a day, every 2232 hours	2	2
Twice a day, every 2244 hours	2	2
Twice a day, every 2256 hours	2	2
Twice a day, every 2268 hours	2	2
Twice a day, every 2280 hours	2	2
Twice a day, every 2292 hours	2	2
Twice a day, every 2304 hours	2	2
Twice a day, every 2316 hours	2	2
Twice a day, every 2328 hours	2	2
Twice a day, every 2340 hours	2	2
Twice a day, every 2352 hours	2	2
Twice a day, every 2364 hours	2	2
Twice a day, every 2376 hours	2	2
Twice a day, every 2388 hours	2	2
Twice a day, every 2400 hours	2	2
Twice a day, every 2412 hours	2	2
Twice a day, every 2424 hours	2	2
Twice a day, every 2436 hours	2	2
Twice a day, every 2448 hours	2	2
Twice a day, every 2460 hours	2	2
Twice a day, every 2472 hours	2	2
Twice a day, every 2484 hours	2	2
Twice a day, every 2496 hours	2	2
Twice a day, every 2508 hours	2	2
Twice a day, every 2520 hours	2	2
Twice a day, every 2532 hours	2	2
Twice a day, every 2544 hours	2	2
Twice a day, every 2556 hours	2	2
Twice a day, every 2568 hours	2	2
Twice a day, every 2580 hours	2	2
Twice a day, every 2592 hours	2	2
Twice a day, every 2604 hours	2	2
Twice a day, every 2616 hours	2	2
Twice a day, every 2628 hours	2	2
Twice a day, every 2640 hours	2	2
Twice a day, every 2652 hours	2	2
Twice a day, every 2664 hours	2	2
Twice a day, every 2676 hours	2	2
Twice a day, every 2688 hours	2	2
Twice a day, every 2700 hours	2	2
Twice a day, every 2712 hours	2	2
Twice a day, every 2724 hours	2	2
Twice a day, every 2736 hours	2	2
Twice a day, every 2748 hours	2	2
Twice a day, every 2760 hours	2	2
Twice a day, every 2772 hours	2	2
Twice a day, every 2784 hours	2	2
Twice a day, every 2796 hours	2	2
Twice a day, every 2808 hours	2	2
Twice a day, every 2820 hours	2	2
Twice a day, every 2832 hours	2	2
Twice a day, every 2844 hours	2	2
Twice a day, every 2856 hours	2	2
Twice a day, every 2868 hours	2	2
Twice a day, every 2880 hours	2	2
Twice a day, every 2892 hours	2	2
Twice a day, every 2904 hours	2	2
Twice a day, every 2916 hours	2	2
Twice a day, every 2928 hours	2	2
Twice a day, every 2940 hours	2	2
Twice a day, every 2952 hours	2	2
Twice a day, every 2964 hours	2	2
Twice a day, every 2976 hours	2	2
Twice a day, every 2988 hours	2	2
Twice a day, every 3000 hours	2	2

Table 2
Correct Interpretation of Prescription Medication Instructions, By Literacy Level

Structured Interview and Literacy Assessment

After obtaining informed consent, a trained RA administered a structured interview that lasted approximately 20 minutes and included a self-report of sociodemographic information (age, gender, race/ethnicity, education, number of prescription medicines taken daily) and a brief literacy assessment. The RA then presented each patient the ten prescription bottles one at a time and asked "How would you take this medicine?" The RA documented patients' verbatim responses. All patients viewed the pill bottles in the same order, which was determined by random assignment. This procedure has been widely used by this research team to assess patients' functional understanding of prescription drug instructions and warnings^{4,7,11}.

Patient responses were independently rated as either correct or incorrect by three general internal medicine attending physicians from two academic medical centers. Physicians were blinded to patient information and were trained to follow stringent coding guidelines previously agreed upon by the research team⁷. Coding was given only if patients' responses included both the proper dose (number of pills to be taken at a time) and frequency of use (number of times drug is to be taken daily) as stated on the label. For labels that detailed a drug's frequency using hourly intervals or time periods, raters followed a predetermined set of acceptable responses for coding purposes to allow for some variability in interpretation. Instructions that included specific times for taking the medicine had to be precise or give a very close approximation.

correct. If frequency was stated using the number of times per day, responses were correct if either 1 number was reported back, or if appropriate specific times or time periods (i.e., 8 A.M., noon, 5 P.M. lunch, dinner) were described. If patients' responses were inaccurate or incomplete in their interpretation, they were scored as incorrect.

Inter-rater reliability between the three physicians coding the patient responses was very high (Kaplan's κ = 0.92). Responses that received discordant ratings between the three reviewers ($n = 252$) were scored by a panel consisting of a primary care physician and two behavioral scientists with expertise in health literacy. Each panel member was blinded to patient information, independently coded the responses as correct or incorrect. A consensus was achieved for 91% of responses. A majority rule was used for the remaining 24 responses.

Literacy Assessment Patient literacy was assessed using the Rapid Estimate of Adult Literacy in Medicine (REALM), a reading recognition test comprised of 66 health related words^{16,17}. The REALM is the most commonly used test of patient literacy in medical settings¹⁸. Raw scores can be converted into one of three reading levels: sixth grade or less (0–46), seventh to eighth (45–60), ninth grade and above (61–66). REALM is highly correlated with other standardized reading tests and the Test of Functional Health Literacy in Adults (TOFHLA)^{18,19}.

Analysis Plan

All statistical analyses were performed using SAS software version 9.1 (Cary, NC). Descriptive statistics (percentage, mean and standard deviation) were calculated for each variable. Chi-square tests were used to evaluate the association between sociodemographic characteristics and patient understanding of each of the ten prescription label instructions. In multivariate analysis, the ten binary repeated responses of correct or incorrect understanding per subject were modeled using a generalized linear model with a complementary log–log link function. A generalized estimating equation (GEE) approach was used to adjust model coefficients and standard errors for within-patient correlation using PROC GENMOD (SAS Institute, Cary, NC). 95% confidence intervals were calculated for adjusted relative risk ratios using the robust estimate of the error as detailed by Liang and Zeger^{20,21}. The final multivariate model included the variables age, gender, race (white vs. African American), education, site, and number of medications currently taken daily. The language used to state frequency of use (times per day, hourly intervals, time periods, specific times) entered in the model as the primary independent variable of interest. The complexity of the instruction (one tablet a day vs. two tablets twice daily) was considered to be a potential risk factor to patient understanding and also entered in the analysis as a covariate. Patient literacy was classified either as low (6th grade or below), marginal (7th–8th grade) or adequate (9th grade and higher). In order to examine whether explicit instructions could overcome the barrier of limited literacy on patient understanding, an interaction term for literacy and type of language used in the instruction was included in the final model.

RESULTS

The mean age of patients was 48.4 years (SD = 13.7; range 20 to 80 years); 72% were female and 61% were African-American. Approximately half of patients were recruited in Shreveport (56%), 25% in New Orleans and 19% in Chicago. Twenty percent of respondents had less than a high school education; 15% were unable to read as reading at or below a 6th grade level (low literacy), and 30% were reading at the 7th–8th grade level.

(marginal literacy). Patients were currently taking an average of 2.8 prescription medications (SD = 1.5). Literacy was associated with older age (< 0.001), African American race (< 0.001), and less education (< 0.001 ; Table 1).

Table 1
Sample Characteristics Stratified by Literacy Level

Each patient provided interpretations for ten different instructions for a total of 3,590 responses for drugs. Of these 839 (23%) were coded as incorrect. Seventy-eight percent of patients misunderstood more instructions, with 37% misunderstanding a minimum of three labels. The prevalence of incorrect interpreting one or more label instructions among patients with adequate, marginal and low literacy 84%, and 93%, respectively (< 0.001). Rates of correct interpretation were lowest for instructions that depicted frequency in hourly intervals or the number of times of day (“Take 1 pill by mouth every 12 hours”, “Take two tablets by mouth twice daily”; 53% and 61%, respectively) and highest for those that depicted time periods (“Take 2 pills in the morning and 2 pills in the evening”, “Take 1 pill by mouth every day”; 89% for both labels).

Patients with low literacy were more likely to misinterpret seven of the ten instructions compared to adequate literacy (Table 2). Two of three label instructions where literacy was not significantly associated with correct interpretations were for atenolol, which had the most basic frequency schedule (1 tablet a day). Statistically significant differences in rates of understanding the medication labels were noted by either the number of prescription medications currently taken by patients.

In multivariate analyses, prescription instructions that gave time periods (morning, evening) or specific times (8 A.M. and 5 P.M.) were significantly less likely to be misinterpreted compared to those using the number of times per day [twice daily] (time period — adjusted relative risk ratio (ARR) 0.42, 95% confidence interval (CI) 0.34–0.52; specific times — ARR 0.60, 95% CI 0.49–0.74; Table 3). Frequency of use stated in hourly intervals (i.e., every 12 hours) was significantly more likely to be misinterpreted compared to writing frequency as number of times per day (ARR 2.87, 95% CI 2.29–3.60). The reference group was then altered from previous times per day to time periods in order to determine if this latter format significantly improved comprehension compared to the use of specific times. Misinterpretation of instructions was higher for specific times compared to time periods (ARR 1.43, 95% CI 1.19–2.71).

Table 3
Generalized Estimating Equation (GEE) Model^a for Misunderstanding Prescription Medication Label Instructions

Low and marginal literacy were also statistically significant independent predictors of misinterpreting instructions (low — ARR 2.70, 95% CI 1.81–4.03; marginal — ARR 1.66, 95% CI 1.18–2.32). Fewer years of education ($< high school$, ARR 1.36, 95% CI 1.03–1.77) and greater dose complexity (four tablets taken [glyburide]); ARR 1.47, 95% CI 1.20–1.83) were also found to be significantly and independently associated with misinterpretation.

with misinterpretation. The interaction term for literacy and type of language used to depict drug frequency was included in the final multivariate model; it approached but did not reach statistical significance (OR 0.91, 95% CI 0.85–1.01; $p = 0.079$).

DISCUSSION

Physicians may assume patients can interpret prescription drug label instructions, yet four out of five (79%) in this study misinterpreted one or more of the ten common prescription label instructions they encountered. Although the instructions were brief and of minimal reading difficulty, rates of patient understanding varied widely across all literacy levels. More explicit language instructing patients with the medicine using time periods were better understood compared to instructions that more vaguely stated number of times per day or hourly intervals. This finding is supported by prior research demonstrating that older adults have greater difficulty interpreting medication instructions that do not explicitly detail when to take a prescribed medicine^{13–15}.

Labels that instruct patients to take medications “twice daily” or “every 12 hours” require patients to take additional mental steps to infer when to take a medicine. For patients with limited literacy, this adds an unnecessary cognitive burden, resulting in poorer comprehension¹². Despite the use of more precise instructions, however, comprehension among those with low literacy skills was still significantly lower than among patients with marginal or adequate literacy skills. This is also not surprising, as earlier health literacy research found that materials with low reading grade levels were likely to improve comprehension among patients with adequate literacy, but had only variable success in improving comprehension among patients with low literacy²².

Interestingly, identifying specific times each day (8 A.M., 5 P.M.) for administration was a more easily understood instruction format than stating times per day or hourly intervals. However, patients were significantly more likely to misinterpret these instructions compared to those stating time periods in general (morning, evening). It is possible that patients do not need such precision when following medication instructions. Stating frequency using time periods of day rather than precise times may better reflect patient preference to tailor the implementation of their drug regimens to their daily schedule. Also of note, more complex dose regimens requiring patients to take more pills a day was a significant independent predictor of misinterpretation of instructions. A prescription requiring a patient to take four pills a day was 47% more likely to be misinterpreted than instructions for a ‘one-a-day’ regimen. Patients with low literacy did not differ significantly from those with adequate literacy in interpreting instructions to take one pill a day, or in understanding “Take 2 pills by mouth every day” and “Take 1 with breakfast and 1 with supper.” Although the latter instruction involved taking pills two times daily, the label broke down the instructions for dose and frequency and provided a context for the time of day.

The limitations to our study should be noted. First, we investigated patient understanding of different types of writing instructions included on the primary label for prescription medications only. The association between misunderstanding of these instructions and medication error was not examined. We also did not study patients’ actual prescription drug-taking behaviors. Patients’ motivation, concentration and comprehension might have been greater if they were reporting on their own medicine given by their physician for conditions they or their children actually had^{14,23,24}. Second, since the study design did not include a chart review

not have information on patients' health information; in particular whether they had actual experience with the study medications. Third, we primarily manipulated the language for frequency of use; however, more subtle differences in word choice and numeric presentation of dose on the various drug instructions may also have altered patients' understanding. Fourth, patients in our study were mostly socioeconomically disadvantaged individuals from three primary care clinics in diverse areas of the country. Our sample addresses those individuals disproportionately affected by poor health outcomes, and whose health was targeted for improvement by Healthy People 2010²⁵. Finally, the generalizability of our findings are limited by the fact that patients were predominantly female (an accurate depiction of the clinic patient populations), and that participation was limited to patients who spoke English. This was due in part to using the Rapid Estimate of Adult Literacy in Medicine (REALM) as our literacy assessment.

While further improvements might be made in the design of prescription drug labels, it is likely that counseling will also be needed to address health literacy deficits. Previous research has found physicians commonly review the instructions when prescribing medications, nor do pharmacists routinely verbally counsel patients when filling a prescription²⁶⁻²⁹. Both the American Medical Association and American Pharmacists Association recommend provider training in health literacy communication 'best practices' a highly efficacious approach described in recent cognitive factors research, known as "implementation intention" might also aid provider training activities³¹. This could be a promising health literacy strategy at the provider level, as it refers to a process of helping patients visualize exactly how a prescribed medication should be self-administered within the context of their own daily routine. As minimal standards exist to guide physician and pharmacist best practices for writing and transcribing the dose and frequency of use on label instructions for patients, both professionals should make it their goal to be simple, clear and explicit in directing patients on how to self-administer their medication.

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Conflict Of Interest None disclosed.

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Report of the Task Force on Uniform Prescription Labeling Requirements

Members Present:

Michael J. Romano (PA), *chair*; Barry J. Boudreaux (NV); Karen DiStefano (RI); Patricia Donato (NY); Virginia Herold (CA); Ronald Huether (SD); William Prather (GA); Leo H. Ross (VA)

Others Present:

Karen M. Ryle, *executive committee liaison*; Carmen Catizone, Melissa Madigan, Larissa Doucette, *NABP staff*

Guests:

Colleen Brennan, *United States Pharmacopeia*; Darren K. Townzen, *National Council for Prescription Drug Programs*

The Task Force on Uniform Prescription Labeling Requirements met December 6, 2008 at the JW Marriott Starr Pass Hotel, Tucson, AZ.

This task force was established in response to Resolution 104-3-08, Task Force on Uniform Prescription Labeling Requirements, which was approved by the NABP membership at the Association's 104th Annual Meeting in May 2008.

Review of the Task Force Charge

Task force members reviewed their charge and accepted it as follows:

1. Evaluate current state and federal laws and regulations addressing prescription label format and content.
2. Review the results of the findings of both state and federal studies regarding prescription labeling.
3. Study the feasibility of implementing standardized state requirements for prescription label format and content and for patient medication information.
4. Recommend revisions, if necessary, to the Model State Pharmacy Act and Model Rules of the National Association of Boards of Pharmacy (*Model Act*) addressing these issues so as to increase readability and comprehension of labels by patients.

Recommendation 1: Endorse and disseminate statement on prescription labeling.

The task force recommends that the NABP Executive Committee endorse the following statement on the issue of prescription labeling and disseminate it to all interested stakeholders:

The purpose of the prescription label is to provide critical information to the patient so that he or she may use the medication appropriately and comply with the medication regimen. The label should be patient-centered. The label should not be used as an audit mechanism by third-party payers, nor should it be used for promotional purposes by dispensing pharmacies. Further, the label should not be used as a sole means to determine compliance with pharmacy laws and regulations by pharmacy regulators.

The prescription label cannot and should not replace critical pharmacist care responsibilities, such as appropriately identifying the patient at the time of dispensing and providing patient counseling.

Background:

Upon review and discussion of the issue of prescription labeling and concerns related to patients' understanding of such labeling, the task force determined it is important to clearly identify for what purposes prescription labels should and should not be used. As stated above, members felt that labels should be used solely to provide patients with important information about medication use. They agreed that prescription labels should not replace critical pharmacist care responsibilities. Identified were two such primary responsibilities: patient identification and patient counseling. On these issues, the task force stated the following:

1. Patient Identification – Patient data elements, such as address, are important identifiers but do not warrant inclusion on the label; instead, such information should be contained in other patient identification systems upon which a pharmacist relies to ensure that the patient receives his or her medication and to avoid confusion among patients with similar names or whose names may bear suffixes such as “Jr” or “Sr” within a family group.
2. Patient Counseling – The single most effective component to increase and improve patient compliance and avoid medication errors, as documented in numerous studies, is appropriate patient counseling. The prescription label is designed to supplement this critical pharmacist responsibility and not replace it in any way. Pharmacists cannot avoid their legal and professional responsibilities by deferring counseling activities to the prescription label. Further, boards of pharmacy cannot regulate counseling activities through the prescription label.

Recommendation 2: Amend the NABP Model Act language addressing prescription drug labeling.

The task force recommends that NABP Executive Committee approve amendments to the *Model Act* that will ensure prescription labels are organized in a patient-centered manner and that mandate the following data elements appear on the prescription label. The task force has consciously removed some data elements historically included on prescription labels to make room for the most critical patient information.

- A. Critical Information for Patients – Critical information must appear on the label with emphasis (highlighted or bolded), in a sans serif (such as “arial”), minimum 12-point

font, and in “sentence case.” Field size and font size may be increased in the best interest of patient care. Critical information text should never be truncated.

- a. Patient name.
 - i. Legal name of the patient. If patient is an animal, include the last name of the owner, name of the animal, and animal species.
 - b. Directions for use.
 - i. The directions for use as indicated by the prescriber and medication purpose/indication if included on prescription drug order.
 1. Boards of pharmacy and licensees should recognize that “take as directed” may not provide sufficient information for the appropriate use of the medication. “Take as directed” is appropriate when specific directions are included on a unit-of-use package or dispensed package or in situations when directions are not able to be included on the label and the pharmacist presents directions to the patient and documents that such directions were given. “Take as directed” should not be used in lieu of patient counseling.
 2. It is understood that prescription drug orders often do not include the indication for use.
 - ii. Language should be simplified, avoiding unfamiliar words and medical jargon; when applicable, use numeric instead of alphabetic characters.
 - c. Drug name.
 - i. Name of the drug.
 - ii. If written for a brand name and a generic drug is dispensed, include phrase “Generic for [brand name].”
 - iii. If a fixed combination generic product is dispensed, use the United States Pharmacopeia (USP) publication of Pharmacy Equivalent Names (PEN) abbreviation. If no PEN has been officially issued by the USP, label the medication *secundum artem*.
 - iv. Include drug name suffixes, such as CD, SR, XL, XR, etc.
 - d. Drug strength.
 - i. Strength of the drug.
 - e. “Use by” date.
 - i. Date by which medication should be used; not expiration date of medication or expiration date of prescription.
 - ii. Format as: “Use by: MM/DD/YY.”
- B. Important Information for Patients – Must appear on the label but should not supersede Critical Information for Patients.
- a. Pharmacy name.
 - i. Name of the dispensing pharmacy. Boards of pharmacy should recognize that some pharmacies “do business as” a name other than the corporate name.
 - b. Pharmacy telephone number.
 - i. Phone number of the dispensing pharmacy. Recognizing that a central fill pharmacy may be involved in the filling process, boards of pharmacy should not require more than one telephone number on the label.

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- c. Prescriber name.
 - i. Name of the prescriber.
 - ii. Format – “Prescriber: [prescriber name].”
- d. “Fill date.”
 - i. Date the prescription is dispensed, which will change with each subsequent refill. Format – “Date filled: MM/DD/YY.”
 - ii. The “fill date” and “use by” date should be the only dates appearing on the prescription label. Other dates often found on labels, such as the original and expiration dates of the prescription drug order can be misunderstood by patients and clutter the label with unnecessary information.
 - iii. The term “fill date” should be defined in the *Model Act*.
- e. Prescription number.
 - i. Identifies the number of the pharmacy record under which the prescription information is recorded.
- f. Drug quantity.
 - i. Quantity of drug dispensed.
 - ii. Format – “Qty: [number].”
- g. Number of refills.
 - i. Number of remaining refills.
 - ii. Format – “Refills: [number remaining]” or “No refills,” using whole numbers only and managing partial fills through the pharmacy recordkeeping system.
- h. Product description.
 - i. Written or graphic description of medication dosage form.
- i. Auxiliary information.
 - i. Auxiliary labels – information should be evidence based, standardized, and demonstrated to complement the prescription label.

Examples of compliant labels include the following:

Pharmacy Name:	Date Filled: MM/DD/YY	Cautions:
Phone:	Rx No.:	
Purpose:		Description:
Patient Q. Name		
Prescriber:		
Take 1 tablet in the morning and 2 tablets at bedtime.		
Drug Name and Strength		
Generic for:	Qty:	
Use by: MM/DD/YY	Refills:	

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Pharmacy Name: Phone: Patient Q. Name Rx No.: Date Filled: MM/DD/YY Prescriber: Drug Name and Strength Generic for: Qty: Refills: Use by: MM/DD/YY	Purpose: Take 1 tablet in the morning and 2 tablets at bedtime. Cautions: Description:
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Recommendation 3:

The task force recommends that NABP work with federal and state agencies and pharmacy stakeholders to advocate for and ultimately achieve changes in state or federal laws and regulations and industry standards to support a patient-centered label.

Background:

The task force recognized that Recommendation 2 represents a significant change in the philosophy of what defines a prescription label and the purpose of the prescription label. In some situations, this recommendation will be contrary to existing federal and state laws and regulations and industry standards. The *Model Act* cannot and is not intended to contravene state and/or federal laws or regulations. The task force understands this and supports NABP working with relevant agencies and organizations to allow the use of a patient-centered label.

Recommendation 4:

The task force recommends that the NABP Executive Committee approve amendments to the *Model Act* to note that the following additional data elements may appear on the prescription label:

- Bar codes
- Pharmacy address
- Pharmacy store number

Background:

The task force wanted to give states the option to allow pharmacies to include these elements on the label if they felt they were necessary.

Recommendation 5:

The task force recommends that NABP work with relevant organizations, including the American Medical Association, the Federation of State Medical Boards, and the Centers for Medicare and Medicaid Services (CMS), to require that medication indications be included on all prescriptions including but not limited to written and electronic prescription drug orders.

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Background:

Task force members agreed that this item of information is vital for appropriate medication counseling. It was felt that this was a good time to approach CMS about the possibility of requiring prescribers to include such information in order to be reimbursed for their services.

Attachment 2c

Arizona Pharmacy Act

Title 32, Ch. 18

32-1963.01. Substitution for prescription drugs; requirements; label; definitions

A. If a medical practitioner prescribes a brand name drug and does not indicate an intent to prevent substitution as prescribed in subsection D of this section, a pharmacist may fill the prescription with a generic equivalent drug.

B. Any pharmacy personnel shall notify the person presenting the prescription of the amount of the price difference between the brand name drug prescribed and the generic equivalent drug, if both of the following apply:

1. The medical practitioner does not indicate an intent to prevent substitution with a generic equivalent drug.
2. The transaction is not subject to third party reimbursement.

C. The pharmacist shall place on the container the name of the drug dispensed followed by the words "generic equivalent for" followed by the brand or trade name of the product that is being replaced by the generic equivalent. The pharmacist shall include the brand or trade name on the container or label of any contact lenses dispensed pursuant to this chapter.

D. A prescription generated in this state must be dispensed as written only if the prescriber writes or clearly displays "DAW ", "Dispense as written", "do not substitute", "medically necessary" or any statement by the prescriber that clearly indicates an intent to prevent substitution on the face of the prescription form. A prescription from out of state or from agencies of the United States government must be dispensed as written only if the prescriber writes or clearly displays "do not substitute", "dispense as written" or "medically necessary" or any statement by the prescriber that clearly indicates an intent to prevent substitution on the face of the prescription form.

E. This section applies to all prescriptions, including those presented by or on behalf of persons receiving state or federal assistance payments.

F. An employer or agent of an employer of a pharmacist shall not require the pharmacist to dispense any specific generic equivalent drug or substitute any specific generic equivalent drug for a brand name drug against the professional judgment of the pharmacist or the order of the prescriber.

G. The liability of a pharmacist in substituting according to this section shall be no greater than that which is incurred in the filling of a generically written prescription. This subsection does not limit or diminish the responsibility for the strength, purity or quality of drugs provided in section 32-1963. The failure of a prescriber to specify that no substitution is authorized does not constitute evidence of negligence.

H. A pharmacist may not make a substitution pursuant to this section unless the manufacturer or distributor of the generic drug has shown that:

1. All products dispensed have an expiration date on the original package.
2. The manufacturer or distributor maintains recall and return capabilities for unsafe or defective drugs.

I. The labeling and oral notification requirements of this section do not apply to pharmacies serving patients in a health care institution as defined in section 36-401. However, in order for this exemption to apply to hospitals, the hospital must have a formulary to which all medical practitioners of that hospital have agreed and that is available for inspection by the board.

J. The board by rule shall establish a list of drugs that shall not be used by dispensing pharmacists as generic equivalents for substitution.

K. In this section:

1. "Brand name drug" means a drug with a proprietary name assigned to it by the manufacturer or distributor.
2. "Formulary" means a list of medicinal drugs.
3. "Generic equivalent" or "generically equivalent" means a drug that has an identical amount of the same active chemical ingredients in the same dosage form, that meets applicable standards of strength, quality and purity according to the United States pharmacopeia or other nationally recognized compendium and that, if administered in the same amounts, will provide comparable therapeutic effects. Generic equivalent or generically equivalent does not include a drug that is listed by the federal food and drug administration as having unresolved bioequivalence concerns according to the administration's most recent publication of approved drug products with therapeutic equivalence evaluations.

Attachment 2f

ENGLISHSPANISH ♦

Take 1 pill at bedtime	Tome 1 pastilla a la hora de acostarse
Take 2 pills at bedtime	Tome 2 pastillas a la hora de acostarse
Take 3 pills at bedtime	Tome 3 pastillas a la hora de acostarse
Take 1 pill in the morning	Tome 1 pastilla por la mañana
Take 2 pills in the morning	Tome 2 pastillas por la mañana
Take 3 pills in the morning	Tome 3 pastillas por la mañana
Take 1 pill in the morning and 1 pill at bedtime	Tome 1 pastilla por la mañana y Tome 1 pastilla a la hora de acostarse
Take 2 pills in the morning and 2 pills at bedtime	Tome 2 pastillas por la mañana y Tome 2 pastillas a la hora de acostarse
Take 3 pills in the morning and 3 pills at bedtime	Tome 3 pastillas por la mañana y Tome 3 pastillas a la hora de acostarse
Take 1 pill in the morning 1 pill at noon and 1 pill in the evening	Tome 1 pastilla por la mañana, 1 pastilla al mediodía y 1 pastilla al atardecer
Take 2 pills in the morning 2 pills at noon and 2 pills in the evening	Tome 2 pastillas por la mañana, 2 pastillas al mediodía y 2 pastillas al atardecer
Take 3 pills in the morning 3 pills at noon and 3 pills in the evening	Tome 3 pastillas por la mañana, 3 pastillas al mediodía y 3 pastillas al atardecer
Take 1 pill in the morning 1 pill at noon and 1 pill at bedtime	Tome 1 pastilla por la mañana, 1 pastilla al mediodía, 1 pastilla a la hora de acostarse
Take 2 pills in the morning 2 pills at noon and 2 pills at bedtime	Tome 2 pastillas por la mañana, 2 pastillas al mediodía, 2 pastillas a la hora de acostarse
Take 3 pills in the morning 3 pills at noon and 3 pills at bedtime	Tome 3 pastillas por la mañana, 3 pastillas al mediodía, 3 pastillas a la hora de acostarse

ENGLISHCHINESE ♦

Take 1 pill at bedtime	睡前服一粒藥丸
Take 2 pills at bedtime	睡前服兩粒藥丸
Take 3 pills at bedtime	睡前服三粒藥丸
Take 1 pill in the morning	早上服一粒藥丸
Take 2 pills in the morning	早上服兩粒藥丸
Take 3 pills in the morning	早上服三粒藥丸
Take 1 pill in the morning and 1 pill at bedtime	早上服一粒藥丸和 睡前服一粒藥丸
Take 2 pills in the morning and 2 pills at bedtime	早上服兩粒藥丸和 睡前服兩粒藥丸
Take 3 pills in the morning and 3 pills at bedtime	早上服三粒藥丸和 睡前服三粒藥丸
Take 1 pill in the morning 1 pill at noon and 1 pill in the evening	早上服一粒藥丸 中午服一粒藥丸和 傍晚服一粒藥丸
Take 2 pills in the morning 2 pills at noon and 2 pills in the evening	早上服兩粒藥丸 中午服兩粒藥丸和 傍晚服兩粒藥丸
Take 3 pills in the morning 3 pills at noon and 3 pills in the evening	早上服三粒藥丸 中午服三粒藥丸和 傍晚服三粒藥丸
Take 1 pill in the morning 1 pill at noon and 1 pill at bedtime	早上服一粒藥丸 中午服一粒藥丸和 睡前服一粒藥丸
Take 2 pills in the morning 2 pills at noon and	早上服兩粒藥丸 中午服兩粒藥丸和

Rx for a medical near-miss

<http://articles.latimes.com/2013/jun/03/opinion/la-oe-margolius-prescription-drugs-20130603>

Op-Ed

The California Senate is considering a bill to require pharmacies to dispense medicine with translated instructions in other languages.

June 03, 2013 | By David Margolius

Los Angeles Times

The Legislature is considering a bill -- SB 204 -- that, if passed, would... (William Thomas Cain / Getty...)As the saying goes, "With great power comes great responsibility." That applies to physicians when prescribing medications, but it also should apply to pharmacies when they're dispensing medications.

In December, after seven years of exams, lectures and rounds, I received my medical license. Finally, I had the power to prescribe medications without the co-signature of my supervisor. "Be careful," she advised, "remember the story of 'once.'"

The story of "once" is a cautionary tale that — best as I am able to tell from Google — was adapted from a Spanish soap opera.

In one version, a doctor prescribes a patient a 30-day supply of a medication. Three days later, the patient returns for a refill. "How can this be?" the doctor wonders. The Spanish-speaking patient responds, "I took the pills exactly as the bottle said to: '11 daily.'" The doctor scrutinized the pill bottle: "Take once daily." But "once" read and pronounced "ohn-say" means 11 in Spanish. The patient had taken 11 pills daily, just as the bottle label said — in Spanish.

The patient lives in that story, but in other versions he is hospitalized or even dies. Shortly after I received my license, I had my own version.

Mr. P is a 65-year-old gentleman originally from Mexico. He speaks English well enough to have a light conversation but would be classified as limited English proficient, or LEP. That means he speaks English less than "very well," and he is not unique: 40% of Californians speak a language other than English at home, and more than 6 million Californians are LEP.

He has diabetes, high cholesterol, high blood pressure and coronary artery disease, and takes 10 medications daily. He is a perfect candidate to be one of 150,000 Californians who are sickened or killed each year because of medication errors.

I had hoped to help him. He was taking one blood pressure medication twice a day, so I changed it to the once-a-day formulation. I wrote "Tome 1 pastilla en la noche" on a sticker and stuck it to the bottle to avoid any "once" pitfalls. I felt that this was part of my responsibility as a prescriber of medications.

Three months later, Mr. P ended up in the hospital. He had begun to feel lightheaded a week before, and then he fell. His heart rate in the emergency room was dangerously low. After an extensive evaluation and ultimately a visit to his home by a nurse, we discovered that he had resumed taking his blood pressure medication twice a day, despite being given the new once-a-day formulation. He in effect had doubled the dosage I had prescribed.

The directions I wrote out may have worked, but then he received his first refill and a new pill bottle. Although many pharmacies in California (including some but not all large chains) print non-English directions on pill bottles, his did not.

The Legislature is considering a bill — SB 204 — that would help; it's moved to the Assembly after passage by the state Senate. If it becomes law, pharmacies will be required to print standard medication instructions translated into languages other than English on pill bottles. The instructions are already available in Spanish, Chinese, Vietnamese, Korean and Russian on the Board of Pharmacy's website. With this law, they would be printed on the bottles themselves. (New York has a similar law.)

I, with my power to prescribe, almost killed my patient. Pharmacies, with their power to dispense and advise, could have helped keep him out of the hospital. The Legislature should make this procedure the law.

David Margolius, an internal medicine resident at UC San Francisco, testified before the state Senate Committee of Business and Professions in April in support of SB 204.

Attachment 3

Best Practices for Making Prescription Drug Container Label Information Accessible to Persons Who are Blind or Visually-Impaired or Who are Elderly

Access Board Working Group on Accessible Prescription Drug Container Labels

July 10, 2013

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Legislative Background:

On July 9, 2012, President Obama signed into law the Food and Drug Administration Safety and Innovation Act (Pub. L. 112-144, 126 Stat. 993). The law includes measures to promote drug safety and to improve FDA procedures for reviewing new medicines and medical devices.

A provision of the Act, [Section 904](#), authorizes the Access Board to convene a stakeholder working group to develop best practices for making information on prescription drug container labels accessible to people who are blind or visually-impaired or who are elderly. (See 29 U.S.C. 792.) Under the law, representation within the working group must be divided equally between consumer and industry advocates. The Act exempts the working group from the Federal Advisory Committee Act.

The law calls for the working group to develop, no later than 1 year after the date of the enactment of this Act, best practices for pharmacies to ensure that blind and visually-impaired individuals have safe, consistent, reliable, and independent access to the information on prescription drug container labels.

According to Section 904, the best practices are not mandatory. They are not to be construed as accessibility guidelines or standards of the Access Board, nor do they confer any rights or impose any obligations on working group participants or other persons. The law makes it clear that nothing in Section 904 is to be construed to limit or condition any right, obligation, or remedy available under the Americans with Disabilities Act of 1990 (42 U.S.C. 12101 et seq.) or any other federal or state law requiring effective communication, barrier removal, or nondiscrimination on the basis of disability.

The law also provides that the working group may make this best practices report publicly available through the internet websites of working group participant organizations, and through other means, in a manner that provides access to interested individuals, including individuals with disabilities. The National Council on Disability will conduct an informational and educational campaign in cooperation with the stakeholder working group to inform the public, including people with disabilities and pharmacists, of the best practices. The Government Accountability Office will undertake a review beginning 18 months after the date of this report to assess the extent to which pharmacies are following the best practices and to what extent barriers to information on prescription drug container labels remain.

Working Group Participant Organizations

In October 2012, the Access Board formed an 18-member working group with representation from national organizations advocating for individuals who are blind, visually-impaired, and older adults, as well as industry groups representing retail, mail order, and independent community pharmacies.

The working group is comprised of representatives of the following organizations:

- AARP
- American Council of the Blind (ACB)
- American Foundation for the Blind (AFB)
- Blinded Veterans Association (BVA)
- Council of Citizens with Low Vision International (CCLVI)
- Express Scripts
- Metropolitan Washington Association of the Deaf Blind (MWADB)
- National Association of Chain Drug Stores
- National Community Pharmacists Association
- National Council on Aging (NCOA)
- National Council on Independent Living (NCIL)
- National Federation of the Blind (NFB)
- National Council on Patient Information and Education (NCPiE)
- Rite-Aid
- Target
- US Pharmacopeia (USP)
- Walgreens
- Wal-Mart

The working group met in person in Washington, DC, on January 10 and 11, 2013, and subsequently via five teleconferences. The working group explored various alternatives, including braille, large print labels, and various auditory technologies such as "talking bottles" and radio frequency identification devices. The working group also considered whether there are technical, financial, manpower, or other factors unique to pharmacies with 20 or fewer retail locations which may pose significant challenges to the adoption of the best practices.

Why Are Best Practices Needed?

Persons with visual impairments who cannot read print prescription drug container labels all too often report inadvertently taking the wrong medication, the wrong amount, at the wrong time, and under the wrong instructions, thereby endangering the health and safety of themselves and family members for whom they are caregivers. Without having ready access to their prescription drug container label information, persons with visual impairments are also at risk of taking expired medications, of not being able to obtain refills in a timely manner, and of being unable to detect pharmacy errors. The majority of persons who become blind or visually-impaired do so after age 60, a time when multiple medications are often prescribed and when persons may experience physical and cognitive conditions which heighten the necessity for safe, consistent, reliable, and independent access to prescription drug container label information.

In recent years, various organizations, including US Pharmacopeia (USP), the National Association of Boards of Pharmacy, and the National Council on Patient Information and Education, have recommended the adoption of patient-centered pharmacy practices to improve patient understanding and safe, effective use of prescription medication. Inherently inclusive, patient-centered pharmacy practices promote accessibility, while a one-size-fits-all approach typically creates barriers.

In the context of this report, the term "best practice" refers to a set of working methods that the working group believes is most effective in providing access to prescription drug container label information to customers with blindness and visual impairments, including older adults.

The goal of the best practices for accessible prescription drug container labels is to offer guidance to pharmacies on how to provide accessible prescription drug container labels to patients with visual impairments to enable them to manage their medications independently and privately and have the confidence that they are taking their medications safely, securely, and as prescribed.

What Is a Prescription Drug Container Label?

A prescription drug container label is a legal document that must be prepared by the pharmacist filling the prescription. The pharmacist must ensure the accuracy of the prescription drug container label, and include on the label all elements required by applicable state law.

In 2009, USP determined optimal prescription label content and format to promote safe medication use by critically reviewing factors that promote or distract from patient understanding of prescription drug container label instructions. USP created universal prescription drug container label standards for format, appearance, content, and language (see: [U.S. Pharmacopeial Convention](#)). The best practices in this report build upon the USP universal patient-centered prescription drug container label standards.

Delivery Methods for Providing Accessible Prescription Drug Container Labels

A variety of delivery methods are available for producing accessible prescription drug container labels in audible, braille, and large print formats. Delivery methods include:

- Hard copy braille and large print: A pharmacist filling prescriptions produces hard copy braille and large print labels upon request, and affixes the accessible labels to the prescription drug containers.
- Dedicated electronic equipment: Some equipment is designed specifically to provide accessible prescription drug container labels. Some dedicated electronic methods can be used with containers of various sizes, shapes, and materials. Examples of dedicated electronic methods include:
 - Digital Voice or Text-to-Speech Recorder: This is a small electronic device that a pharmacist affixes to a prescription drug container. When activated by pushing a button on the device, the patient hears the information printed on the prescription drug container label. One device is affixed to each prescription drug container. Some devices also have a USB drive.
 - Radio Frequency Identification Device (RFID): A pharmacist places an RFID tag on a prescription drug container. A patient who is blind or visually-impaired is equipped with a small, dedicated device that, when a container with an RFI Tag is placed over the device, audibly announces the text on the prescription drug container label. This technology may also provide prescription drug container label information in large print, and has a USB drive.
 - Smart devices and computers: Many patients with visual impairments use their own computers and smart devices equipped with electronic braille, large print, and audio technology to access electronic text. Visually impaired computer users, particularly those who are deaf-blind, may request access to prescription drug container labels using their computers and smart devices, either via internet applications (apps) or in combination with dedicated equipment equipped with a USB drive. Methods include pharmacists placing on the prescription drug container a QR code, RFI tag, or other small, electronic unit encoded with the prescription drug container label in electronic text, which visually impaired patients receive on smart devices or computers in electronic braille, large print, or audible format. Note that using this delivery method does not involve pharmacists embossing a braille label; rather, pharmacists use an electronic delivery method that encodes the prescription

drug container label text, which can be displayed via a computer screen, speakers, or an electronic braille display.

Some electronic prescription drug container label delivery methods may also have the capacity to include supplemental information about the prescription medications. In addition, some may have capability to translate prescription drug container label information into several languages.

The key to providing accessible prescription drug container labels is patient-centered communication between pharmacists and patients with blindness and visual impairment and patient representatives. Because the extent of visual impairment varies from person to person, some patients may need prescription drug container labels in an audible format, while others may need braille, and still others may need large print. Additionally, it is important to keep in mind that visually impaired patients who are not computer savvy may need hard copy braille or large print labels, or a dedicated electronic method that is easy to operate.

Best Practices to Use for All Formats

The following best practices promote access to prescription drug container label information in all formats, including audible, braille, and large print labels.

- One of the best things pharmacists can do is to encourage patients and patient representatives to communicate their needs to pharmacists:
 - Advertise a local or, when possible, a toll-free telephone number to promote communication between patients and pharmacists;
 - If pharmacy websites and applications (apps) are made available to patients, ensure website and app accessibility; and
 - When a pharmacist observes a patient or patient representative having reading difficulty, offer education and counseling in a setting that maintains patient privacy.
- Follow universal patient-centered prescription drug container label standards.
- Make available options for accessible prescription drug container labels in audible, braille, and large print formats via methods using, for example, hard copy, dedicated devices, and computers or smart devices.
- Explain to the patient the available accessible prescription drug container label format options, and provide the prescription drug container label in the format option selected by the patient.
- Ensure that duplicate accessible labels preserve the integrity of the print prescription drug container label.
- Subject accessible prescription drug container labels to the same quality control processes used for print labels to ensure accuracy and patient safety.
- Maintain patient privacy in accordance with the Health Insurance Portability and Accountability Act (HIPAA) rules when preparing accessible prescription drug container labels, e.g., record audible labels in a location where patient information cannot be overheard by unauthorized persons.
- In advance, make arrangements to provide accessible prescription drug container labels. For example, maintain a sufficient inventory of supplies necessary to support timely provision of prescription drug container labels in accessible label formats.
- Provide prescription medication with an accessible prescription drug label within the time frame the same prescription would be provided to patients without visual impairments.
- Do not impose a surcharge or extra fee to an individual to cover the cost of providing an accessible drug container label and equipment dedicated for prescription drug container label access.
- Ensure the durability of accessible label format options until the expiration date specified on the prescription drug container label.
- Select a container that best supports the type of accessible label provided.

- For all accessible label formats, including audible formats, ensure that all required information contained on the print prescription drug container label is provided on the accessible label in the same sequence as the print label.
- Include in accessible prescription drug container labels the information on warning labels added to the container at the pharmacist's discretion.

Format-Specific Best Practices

In addition to the best practices listed above, please note the following format-specific best practices.

Audible Prescription Drug Labels

For dedicated equipment, select devices that provide independent, easy to use, start/stop operation, with volume control, and ear bud access for privacy.

If using a voice recorder:

- speak in a clear voice;
- record information in a setting that minimizes background noise and maintains patient privacy.

Offer to show the patient how to operate the audible prescription drug container label.

Braille Prescription Drug Container Labels

Electronic delivery method: Acquire an electronic delivery method using RFI tags, QR codes, or other processes to provide electronic text of the prescription drug container label upon request. Consumers with electronic braille equipment may then access electronic text in braille format.

Note that, as required, the working group considered significant challenges that pharmacies may face in producing drug labels in accessible formats, such as hard copy braille. The working group recognizes that mail order and online pharmacies, because of their centralized structure, large volume, and mail delivery process, may be better equipped than local stores to provide hard copy braille prescription drug container labels. Many mail order and online pharmacies have established a unit with the necessary computer software and braille embossers to produce hard copy braille labels and a protocol to develop pharmacists' proficiency in printing accurate braille labels.

- If a local pharmacy store has a high demand for hard copy braille prescription drug container labels, acquire on-site braille embosser capacity and proficiency.
- If a local pharmacy store receives infrequent or occasional requests for hard copy braille prescription drug container labels, partner with a pharmacy that has braille prescription drug container labeling capacity to provide a hard copy braille prescription drug container label.

When embossing hard copy braille prescription drug container labels:

- Use contracted (Grade 2) braille.
- Emboss braille labels on transparent material in order to preserve the legibility of print container labels. Affix braille label to the prescription drug container with strong adhesive.
- Do not fold braille labels.

Printing Large Print Labels (hard copy):

- Print label in 18-point bold font.
- Use non-glossy paper or other material that is durable and a size that is easy to manipulate.
- Use print with highest possible contrast between text and background color (ideally black text on a white or pale yellow background). If printing on both sides, use material that does not allow print bleed-through from one side to the other.

- Use sentence case, with the initial capital letter followed by lower-case characters.
- Use non-condensed, san-serif font, such as Arial.
- Provide 1.5 line spacing.
- Use horizontal text only.
- Securely affix the large print label to the prescription drug container.
- When covering a large print label with protective tape, use non-glossy, transparent tape.

Resources

[USP Patient-Centered Prescription Label Standards](#)

UMS White Paper, The National Council for Prescription Drug Programs Work Group (WG), 2013

Working Group Participant Organizations

- AARP
- American Council of the Blind (ACB)
- American Foundation for the Blind (AFB)
- Blinded Veterans Association (BVA)
- Council of Citizens with Low Vision International (CCLVI)
- Express Scripts
- Metropolitan Washington Association of the Deaf Blind (MWADB)
- National Association of Chain Drug Stores
- National Community Pharmacists Association
- National Council on Aging (NCOA)
- National Council on Independent Living (NCIL)
- National Council on Patient Information and Education (NCPIE)
- National Federation of the Blind (NFB)
- Rite-Aid
- Target
- US Pharmacopeia (USP)
- Walgreens
- Wal-Mart

Attachment 4

[The Federal Register](#)

The Daily Journal of the United States Government

Proposed Rule

Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products

A Proposed Rule by the [Food and Drug Administration](#) on 11/13/2013

Publication Date:

[Wednesday, November 13, 2013](#)

Agencies:

[Department of Health and Human Services](#)

[Food and Drug Administration](#)

Dates:

Submit either electronic or written comments on the proposed rule by January 13, 2014. See section VII for the proposed effective date of a final rule based on this proposed rule. Submit comments on information collection issues under the Paperwork Reduction Act of 1995 (the PRA) by December 13, 2013, (see the "Paperwork Reduction Act of 1995" section of this document).

Comments Close:

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2013-26799

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Related Topics

- [Administrative practice and procedure](#)
- [Biologics](#)
- [Confidential business information](#)
- [Drugs](#)
- [Reporting and recordkeeping requirements](#)

Action

Proposed Rule.

Summary

The Food and Drug Administration (FDA or the Agency) is proposing to amend its regulations to revise and clarify procedures for application holders of an approved drug or biological product to change the product labeling to reflect certain types of newly acquired information in advance of FDA's review of the change. The proposed rule would create parity among application holders with respect to such labeling changes by permitting holders of abbreviated new drug applications (ANDAs) to distribute revised product labeling that differs in certain respects, on a temporary basis, from the labeling of its reference listed drug (RLD) upon submission to FDA of a "changes being effected" (CBE-0) supplement. The proposed rule describes the process by which information regarding a CBE-0 labeling supplement submitted by a new drug application (NDA) holder, an ANDA holder, or a biologics license application (BLA) holder would be made publicly available during FDA's review of the labeling change and clarifies requirements for all ANDA holders to submit conforming labeling revisions after FDA has taken an action on the NDA or ANDA holder's CBE-0 labeling supplement. The proposed rule also would amend the regulations to allow submission of a CBE-0 labeling supplement for certain changes to the "Highlights of Prescribing Information" for drug products with labeling in the "Physician Labeling Rule" (PLR) format.

Unified Agenda

[Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products](#)

1 action from September 2013

- September 2013

- NPRM

Tables

- [Table 1—Estimated Annual Reporting Burden¹](#)

DATES:

Submit either electronic or written comments on the proposed rule by January 13, 2014. See section VII for the proposed effective date of a final rule based on this proposed rule. Submit comments on information collection issues under the Paperwork Reduction Act of 1995 (the PRA) by December 13, 2013, (see the “Paperwork Reduction Act of 1995” section of this document).

ADDRESSES:

You may submit comments, identified by Docket No. FDA-2013-N-0500 and/or Regulatory Information Number (RIN) [0910-AG94](#), by any of the following methods, except that comments on information collection issues under the PRA must be submitted to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB) (see the “Paperwork Reduction Act of 1995” section of this document).

Electronic Submissions [Back to Top](#)

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways:

- Mail/Hand delivery/Courier (for paper or CD-ROM submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name and Docket No. FDA-2013-N-0500 and RIN [0910-AG94](#) for this rulemaking. All comments received may be posted without change to <http://www.regulations.gov>, including any personal information provided. For

additional information on submitting comments, see the “Comments” heading of the SUPPLEMENTARY INFORMATION section.

Docket: For access to the docket to read background documents or comments received, go to <http://www.regulations.gov> and insert the docket number(s), found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:

Janice L. Weiner, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6304, Silver Spring, MD 20993-0002, 301-796-3601.

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Executive Summary

Purpose of the Regulatory Action

The Federal Food, Drug, and Cosmetic Act (the FD Act) ([21 U.S.C. 301](#) et seq.) and the Public Health Service Act (the PHS Act) ([42 U.S.C. 201](#) et seq.) provide FDA with authority over the labeling for drugs and biological products, and authorize the Agency to enact regulations to facilitate FDA's review and approval of applications regarding the labeling for those products. FDA is proposing to amend its regulations to revise and clarify procedures for application holders to change the labeling of an approved drug or biological product to reflect certain types of newly acquired information in advance of FDA's review of the change through a CBE-0 supplement. The proposed rule would create parity among application holders with respect to these safety-related labeling changes by permitting ANDA holders to distribute revised generic drug labeling that differs in certain respects, on a temporary basis, from the RLD labeling upon submission to FDA of a CBE-0 supplement.

Summary of the Major Provisions of the Regulatory Action

The proposed rule would enable ANDA holders to update product labeling promptly to reflect certain types of newly acquired information related to drug safety, irrespective of whether the revised labeling differs from that of the RLD. An ANDA holder would be required to send notice of the labeling change proposed in the CBE-0 supplement, including a copy of the information supporting the change, to the NDA holder for the RLD at the same time that the supplement to the ANDA is submitted to FDA, unless approval of the NDA has been withdrawn. This proposal would ensure that the NDA holder for the RLD is promptly advised of the newly acquired information that was considered to warrant the labeling change proposed for the drug in the CBE-0 supplement.

If approval of the NDA for the RLD has been withdrawn (for reasons other than safety or effectiveness), FDA's evaluation of the labeling change proposed by the ANDA holder would consider any submissions related to the proposed labeling change from any other application holder for drug products containing the same active ingredient.

To make the safety-related changes to drug labeling described in a CBE-0 supplement readily available to prescribing health care providers and the public while FDA is reviewing the supplement, FDA proposes to establish a dedicated Web page (or, alternatively, to modify an existing FDA Web page) on which FDA would promptly post information regarding the labeling changes proposed in a CBE-0 supplement.

A supplement to an approved ANDA for a safety-related labeling change that is submitted in a prior approval supplement or in a CBE-0 supplement would be approved upon approval of the same labeling change for the RLD. The proposed rule would establish a 30-day timeframe in which all ANDA holders would be required to submit a CBE-0 supplement with conforming labeling changes after FDA approval of a revision to the labeling for the RLD.

The proposed rule also would amend the regulations to allow submission of a CBE-0 labeling supplement for certain changes to the “Highlights of Prescribing Information” for drug products with labeling in the PLR format. This is intended to remove an unnecessary impediment to prompt communication of the most important safety-related labeling changes (e.g., boxed warnings and contraindications) for drug products with labeling in the PLR format.

Finally, FDA regulations provide that FDA may take steps to withdraw approval of an ANDA if the generic drug labeling is no longer consistent with the labeling for the RLD, subject to certain exceptions specified in the regulations. The proposed rule would amend the regulations to add a new exception for generic drug labeling that is temporarily inconsistent with the labeling for the RLD due to safety-related labeling changes submitted by the ANDA holder in a CBE-0 supplement.

Costs and Benefits

The economic benefits to the public health from adoption of the proposed rule are not quantified. By allowing all application holders to update labeling based on newly acquired information that meets the criteria for a CBE-0 supplement, communication of important drug safety information to prescribing health care providers and the public could be improved. The primary estimate of the costs of the proposed rule includes costs to ANDA and NDA holders for submitting and reviewing CBE-0 supplements. The Agency estimates the net annual social costs to be between \$4,237 and \$25,852. The present discounted value over 20 years would be in the range of \$63,040 to \$384,616 at a 3 percent discount rate, and in the range of \$44,890 to \$273,879 at a 7 percent discount rate.

I. Background

A. Drug Labeling

Under the FD Act, the PHS Act, and FDA regulations, the Agency makes decisions regarding the approval of marketing applications, including supplemental applications, based on a comprehensive analysis of the product's risks and benefits under the conditions of use prescribed, recommended, or suggested in the labeling (see [21 U.S.C. 355\(d\)](#); [42 U.S.C. 262](#)).

FDA-approved drug labeling summarizes the essential information needed for the safe and effective use of the drug,¹ and reflects FDA's finding regarding the safety and effectiveness of the drug under the labeled conditions of use. The primary purpose of labeling (commonly referred to as the “package insert” or “prescribing information”) for prescription drugs is to provide health care practitioners with the essential scientific information needed to facilitate prescribing decisions, thereby enhancing the safe and effective use of prescription drug products and reducing the likelihood of medication errors. Prescription drug labeling is directed to health care practitioners, but may include FDA-approved patient labeling (see § 201.57(c)(18) ([21 CFR 201.57\(c\)\(18\)](#)) and [21 CFR 201.80\(f\)\(2\)](#)). The over-the-counter (OTC) *Drug Facts* labeling is directed to consumers and conveys information in a clear, standardized format to enable patient self-selection of an appropriate drug and enhance the safe and effective use of the drug (see [21 CFR 201.66](#)).

All drugs have risks, and health care practitioners and patients must balance the risks and benefits of a drug when making decisions about medical therapy. As a drug is used more widely or under diverse conditions, new information regarding the risks and benefits of a drug may become available. This may include new risks or new information about known risks. Accordingly, all holders of NDAs, ANDAs, and BLAs are required to develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA (see §§ 314.80(b), 314.98(a), and 600.80(b) ([21 CFR 314.80\(b\)](#), 314.98(a), and 600.80(b))). Application holders must promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers, and comply with applicable reporting and recordkeeping requirements (see §§ 314.80(b), 314.98(a), and 600.80(b))). Application holders also must comply with requirements for other postmarketing reports under § 314.81 ([21 CFR 314.81](#)) and [21 CFR 600.81](#) and section 505(k) of the FD Act ([21 U.S.C. 355\(k\)](#)). These requirements include submission of an annual report (including a brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product, and a description of actions the applicant has taken or intends to take as a result of this new information) and, if appropriate, proposed revisions to product labeling (see § 314.81).

When new information becomes available that causes information in labeling to be inaccurate, the application holder must take steps to change the content of its labeling, in accordance with §§ 314.70, 314.97, and 601.12 ([21 CFR 314.70](#), 314.97, and 601.12). All holders of marketing applications for drug products have an ongoing obligation to ensure their labeling is accurate and up-to-date. A drug is misbranded in violation of the FD Act when its labeling is false or misleading, or does not provide adequate directions for use and adequate warnings (see [21 U.S.C. 331\(a\)](#) and (b) and 352(a), (f), and (j)).

B. Current Requirements Related to Changes to Approved Drug Labeling

For most substantive changes to product labeling, an application holder is required to submit a prior approval supplement and receive FDA approval for the change (see §§ 314.70(b) and

601.12(f)(1)). However, in the interest of public health, the regulations permit certain labeling changes based on newly acquired information about an approved drug to be implemented upon receipt by the Agency of a supplemental application that includes the change. These supplements are commonly referred to as “changes being effected supplements” or “CBE-0 supplements” (see §§ 314.70(c)(6)(iii) and 601.12(f)(2)).

The current regulations provide that application holders may submit CBE-0 supplements for the following types of changes to product labeling:

- To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under § 201.57(c);
- To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdose;
- To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product;
- To delete false, misleading, or unsupported indications for use or claims for effectiveness; or
- Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision.

The CBE-0 supplement procedures originated from a 1965 policy based on FDA's enforcement discretion regarding certain labeling changes that should be placed into effect “at the earliest possible time” (see “Supplemental New-Drug Applications,” 30 FR 993, January 30, 1965). Over the years, FDA has clarified the types of labeling changes that may be made by a CBE-0 supplement through a series of rulemakings.

In 1985, FDA updated its procedures for CBE-0 supplements and emphasized that CBE-0 supplements were intended as a narrow exception to the general rule that labeling changes require FDA's prior approval (see “New Drug and Antibiotic Regulations”; final rule, 50 FR 7452 at 7470, February 22, 1985).

In 2006, FDA amended its regulations governing the content and format of prescription drug labeling to require, among other things, that the labeling of new and recently approved products include introductory prescribing information titled “Highlights of Prescribing Information” (see [21 CFR 201.57\(a\)](#); see also “Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products”; final rule, [71 FR 3922](#), January 24, 2006). The “Highlights of Prescribing Information” (Highlights) is intended to summarize the information that is most important for prescribing the drug safely and effectively, and to organize the information into logical groups to enhance accessibility, retention, and access to the more detailed information (see [71 FR 3922](#) at 3931). As part of this rulemaking, FDA amended the CBE-0 labeling supplement provisions to exclude most changes to the information required in the Highlights, which must be made by a prior approval supplement unless FDA specifically requests that the labeling change be submitted in a CBE-0 supplement or FDA grants a waiver request under § 314.90 ([21 CFR 314.90](#)).

In 2008, FDA amended the regulations governing CBE-0 supplements to codify the Agency's view that a CBE-0 labeling supplement is appropriate only to reflect newly acquired information and to clarify that a CBE-0 supplement may be used to add or strengthen a contraindication, warning, precaution, or adverse reaction only if there is sufficient evidence of a causal association with the approved product. FDA explained that these requirements are intended to help ensure that scientifically accurate information appears in the approved labeling for such products (“Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices”; final rule, [73 FR 49603](#) at 49604, August 22, 2008).

FDA carefully reviews any labeling change proposed in a CBE-0 supplement, as well as the underlying information or data supporting the change. FDA has the authority to accept, reject, or request modifications to the proposed changes as the Agency deems appropriate, and has the authority to bring an enforcement action if the added information makes the labeling false or misleading (see [21 U.S.C. 352\(a\)](#)). If the newly acquired information changes the benefit/risk balance for the drug, such that the product no longer meets FDA's standard for approval, then FDA will take appropriate action (see [21 U.S.C. 355\(e\)](#) and 355-1).

The CBE-0 supplement regulations allow application holders to comply with the requirement to update labeling promptly to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug (§ 201.57(c)(6)), and other risk information as required by the regulations (§§ 201.57(c) and 201.100(d)(3)).

C. Specific Labeling Requirements Related to Generic Drugs

The FD&C Act describes different routes for obtaining approval of two broad categories of drug applications: An NDA containing full reports of investigations of safety and effectiveness, for which the requirements are set out in section 505(b) and (c) of the FD&C Act, and an ANDA, for which the requirements are set out in section 505(j).

The ANDA category can be further subdivided into an ANDA and a “petitioned ANDA.” An ANDA must contain information to show that the proposed drug product is the same as a drug previously approved under section 505(c) of the FD&C Act (the RLD) with respect to active ingredient(s), dosage form, route of administration, strength, labeling, and conditions of use, among other characteristics, and is bioequivalent to the RLD. An applicant that can meet the requirements under section 505(j) of the FD&C Act for approval may rely upon the Agency's finding of safety and effectiveness for the RLD and need not repeat the extensive nonclinical and clinical investigations required for approval of an NDA submitted under section 505(b)(1) of the FD&C Act. A “petitioned ANDA” is a type of ANDA for a drug that differs from a previously approved drug product in dosage form, route of administration, strength, or active ingredient (in a product with more than one active ingredient), for which FDA has determined, in response to a suitability petition submitted under section 505(j)(2)(C) of the FD&C Act, that clinical studies are not necessary to demonstrate safety and effectiveness.

A generic drug is classified as therapeutically equivalent to the RLD if it is a pharmaceutical equivalent and has demonstrated bioequivalence (see “Approved Drug Products With Therapeutic Equivalence Evaluations” (the Orange Book), 33rd ed., 2013, p. vii). The generic

drug program is based on the principle that “products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product” (Orange Book, 33rd ed., 2013, p. vii). Currently, approximately 80 percent of all drugs dispensed are generic drugs (Ref. 1). After the introduction of a generic drug, the market share of the “brand name” drug (i.e., the drug approved in an NDA under section 505(c) of the FD&C Act) may drop substantially. Among drugs for which a generic version is available, approximately 94 percent are dispensed as a generic (Ref. 1). For any given brand name drug, there may be multiple approved generic drugs, and the prescribing health care provider ordinarily would not know which generic drug may be substituted for the prescribed product under applicable State law.

A generic drug is required to have the same labeling as the RLD at the time of approval, except for changes required because of differences approved under a suitability petition (see section 505(j)(2)(C) of the FD Act and [21 CFR 314.93](#)) or because the drug product and the RLD are produced or distributed by different manufacturers (see section 505(j)(2)(A)(v) of the FD Act). FDA has described those differences in § 314.94(a)(8)(iv) ([21 CFR 314.94\(a\)\(8\)\(iv\)](#)) as including, for example, differences in formulation, bioavailability, or pharmacokinetics; labeling revisions made to comply with current FDA labeling guidelines or other guidance; or omission of an indication or other aspect of labeling protected by patent or exclusivity. FDA has generally taken the position that a generic drug must maintain the same labeling as the RLD throughout the lifecycle of the generic drug product (see § 314.150(b)(10) ([21 CFR 314.150\(b\)\(10\)](#))). Thus, if an ANDA holder believes that newly acquired safety information should be added to its product labeling, it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic drug(s) and the RLD should be revised (see 57 FR 17950 at 17961; April 28, 1992).

Although FDA has expressed differing views on this issue over the years, FDA generally has advised that an ANDA holder may use the CBE-0 supplement process only to update its product labeling to conform with approved labeling for the RLD or to respond to FDA's specific request to submit a labeling change under this provision, and may not unilaterally change ANDA labeling in a manner that differs from the RLD (see § 314.150(b)(10); see also 57 FR 17950 at 17961, and “Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices”; proposed rule, [73 FR 2848](#) at 2849; footnote 1; January 16, 2008).

At the time of FDA's adoption of the generic drug regulations in 1992, FDA believed it was important that product labeling for the RLD and any generic drugs be the same to assure physicians and patients that generic drugs were, indeed, equivalent to their RLD. However, as the generic drug industry has matured and captured an increasing share of the market, tension has grown between the requirement that a generic drug have the same labeling as its RLD, which facilitates substitution of a generic drug for the prescribed product, and the need for an ANDA holder to be able to independently update its labeling as part of its independent responsibility to ensure that the labeling is accurate and up-to-date. In the current marketplace, in which approximately 80 percent of drugs dispensed are generic and, as we have learned, brand name drug manufacturers may discontinue marketing after generic drug entry, FDA believes it is time to provide ANDA holders with the means to update product labeling to reflect data obtained

through postmarketing surveillance, even though this will result in temporary labeling differences among products. In a study of FDA safety-related drug labeling changes made in 2010, FDA found that the median time from initial approval of the drug product to the time of making the safety-related labeling change was 11 years, which confirms that data supporting labeling changes may become available after approval of generic versions of the drug product (see Ref. 2). FDA found that “[t]he most critical safety-related label changes, boxed warnings and contraindications, occurred a median 10 and 13 years after drug approval (and the range spanned from 2 to 63 years after approval), underscoring the importance of persistent and vigilant postmarket drug safety surveillance” (Ref. 2).

D. Recent Court Decisions

In two recent cases, the United States Supreme Court considered the issue of whether Federal law preempts State law tort claims against pharmaceutical manufacturers for failing to provide adequate warnings in drug product labeling (“failure-to-warn claims”) (see *Pliva, Inc. v. Mensing*, 131 S.Ct. 2567 (2011) and *Wyeth v. Levine*, 555 U.S. 555 (2009)). In *Pliva v. Mensing*, the Court held that the difference between NDA and ANDA holders' ability to independently change product labeling through CBE-0 supplements leads to different outcomes on whether Federal labeling requirements preempt State law failure-to-warn claims. In *Wyeth v. Levine*, the Court decided that Federal law does not preempt a State law failure-to-warn claim that a brand name drug's labeling did not contain an adequate warning. The Court found that the drug manufacturer could have unilaterally added a stronger warning to product labeling under the CBE-0 regulation as applied to NDAs, and absent clear evidence that FDA would not have approved such a labeling change, it was not impossible for the manufacturer to comply with both Federal and State requirements. The Court reaffirmed that “through many amendments to the [FD&C Act] and to FDA regulations, it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times” (555 U.S. at 570-571).

Two years later, in *Pliva v. Mensing*, the Court decided that Federal law does preempt a State law failure-to-warn claim that a generic drug's labeling did not contain an adequate warning. The Court deferred to FDA's interpretation of its CBE-0 supplement and labeling regulations for ANDAs, and found that Federal law did not permit a generic drug manufacturer to use the CBE-0 supplement process to unilaterally strengthen warnings in its labeling or to issue additional warnings through “Dear Health Care Professional” letters, which FDA “argues . . . qualify as 'labeling' ” (131 S.Ct. at 2576). The Court found that, under the current regulatory scheme, it was impossible for a generic drug manufacturer to comply with its Federal law duty to have the same labeling as the RLD and satisfy its State law duty to provide adequate labeling (131 S.Ct. at 2578). In September 2011, Public Citizen petitioned the Agency to revise its regulations in response to the *Mensing* decision (see Docket No. FDA-2011-P-0675).

As a result of the decisions in *Wyeth v. Levine* and *Pliva v. Mensing*, an individual can bring a product liability action for failure to warn against an NDA holder, but generally not an ANDA holder, and thus access to the courts is dependent on whether an individual is dispensed a brand name or generic drug. The *Mensing* decision alters the incentives for generic drug manufacturers

to comply with current requirements to conduct robust postmarketing surveillance, evaluation, and reporting, and to ensure that the labeling for their drugs is accurate and up-to-date.

We are proposing to change our regulations to expressly provide that ANDA holders may distribute revised labeling that differs from the RLD upon submission of a CBE-0 supplement to FDA. FDA's proposed revisions to its regulations would create parity between NDA holders and ANDA holders with respect to submission of CBE-0 supplements for safety-related labeling changes based on newly acquired information. This proposal is also intended to ensure that generic drug companies actively participate with FDA in ensuring the timeliness, accuracy, and completeness of drug safety labeling in accordance with current regulatory requirements. If this proposed regulatory change is adopted, it may eliminate the preemption of certain failure-to-warn claims with respect to generic drugs.

II. Description of the Proposed Rule

A. Supplement Submission for Safety-Related Labeling “Changes Being Effected” (Proposed §§ 314.70(b)(2), (c)(6), and (c)(8) and 601.12(f)(2))

1. Equal Applicability to NDA Holders and ANDA Holders (Proposed § 314.70(c)(8))

We are proposing to add § 314.70(c)(8) to enable ANDA holders to submit a CBE-0 supplement for generic drug labeling that differs from the labeling of the RLD and to establish that § 314.70(c)(6)(iii) applies equally to the holder of an approved NDA or ANDA. Proposed § 314.70(c)(8) states that an application holder may submit to its approved NDA or ANDA a supplement described by § 314.70(c)(6)(iii).

If an NDA holder or ANDA holder obtains or otherwise receives newly acquired information that should be reflected in product labeling to accomplish any of the objectives specifically described in § 314.70(c)(6)(iii)(A) through (c)(6)(iii)(D), the NDA holder or ANDA holder must submit a CBE-0 supplement (see § 314.70(c)(6)(iii); see also [21 CFR 314.3\(b\)](#) (defining “newly acquired information”). As discussed in section I.A, all application holders, including ANDA holders, are required to conduct surveillance, evaluation, and reporting of postmarketing adverse drug experiences and, if warranted, to propose revisions to product labeling. Proposed § 314.70(c)(8) would expressly permit ANDA holders to update product labeling promptly to reflect newly acquired information that meets the criteria described in § 314.70(c)(6)(iii)(A) through (c)(6)(iii)(D) irrespective of whether the revised labeling differs from that of the RLD. In addition, if an ANDA holder submits a CBE-0 supplement for a labeling change that meets the criteria described in § 314.70(c)(6)(iii)(A) through (c)(6)(iii)(E), the ANDA holder may distribute a “Dear Health Care Provider” letter (which also meets the statutory definition of “labeling”) regarding this labeling change in the same manner as an NDA holder or BLA holder, and be subject to the same statutory prohibition against marketing a misbranded product (see [21 U.S.C. 321\(m\)](#), 331(a) and (b), and 352, and [21 CFR 201.100\(d\)\(1\)](#) and [202.1\(l\)\(2\)](#)). A “Dear Health Care Provider” letter may be used to disseminate the important new drug safety information that warranted the CBE-0 supplement, for example, a significant hazard to health or other important change in product labeling (see [21 CFR 200.5](#)). FDA will continue to undertake any communication plans to health care providers (including distribution of “Dear Health Care

Provider” letters) that are part of Risk Evaluation and Mitigation Strategies (REMS) that include one or more generic drugs (see [21 U.S.C. 355-1\(i\)\(2\)](#)).

The obligation to ensure that labeling is accurate and up-to-date applies equally to all ANDA holders. In certain circumstances, if the RLD approved under section 505(c) of the FD&C Act has been withdrawn from the market, FDA may select a drug product approved in an ANDA (including a petitioned ANDA) to be the “reference standard” that an applicant seeking approval of an ANDA that relies upon the withdrawn RLD must use in conducting an in vivo bioequivalence study required for approval (see 57 FR 17950 at 17954). However, the duty to maintain accurate product labeling does not differ between an ANDA designated as the reference standard for bioequivalence studies and other approved ANDAs.

FDA acknowledges that there may be concerns about temporary differences in safety-related labeling for drugs that FDA has determined to be therapeutically equivalent, especially if multiple ANDA holders submit CBE-0 supplements with labeling changes that differ from each other and from the RLD. FDA also recognizes that health care practitioners are unlikely to review product labeling for each of the generic drugs that may be substituted for the prescribed product when making treatment decisions with their patients based on the balance of potential benefits and risks of the drug product for that patient. To address these concerns, FDA proposes to establish a dedicated Web page (or, alternatively, to modify an existing FDA Web page) on which FDA would promptly post information regarding the labeling changes proposed in a CBE-0 supplement while FDA is reviewing the supplement (see proposed §§ 314.70(c)(8) and 601.12(f)(2)(iii)). The public may subscribe to FDA's free email subscription service to receive an email message each time there is an update to this proposed FDA Web page.

The FDA Web page would provide information about pending CBE-0 supplements for safety-related labeling changes, including but not limited to: The active ingredient, the trade name (if any), the application holder, the date on which the supplement was submitted, a description of the proposed labeling change and source of the information supporting the proposed labeling change (e.g., spontaneous adverse event reports, published literature, clinical trial, epidemiologic study), a link to the current labeling for the drug product containing the changes being effected, and the status of the pending CBE-0 supplement (e.g., whether FDA is reviewing the proposed labeling change, has taken an action on the CBE-0 supplement, or has determined that the supplement does not meet the criteria for a CBE-0 supplement). It is expected that a valid safety concern regarding a generic drug product also would generally warrant submission of a supplement for a change to the labeling by the NDA holder for the RLD, as well as other ANDA holders. The CBE-0 supplements would remain posted on FDA's Web page until FDA has completed its review and issued an action letter. If the CBE-0 supplement is approved, the final approved labeling will be made available on the proposed FDA Web page through a link to FDA's online labeling repository at <http://labels.fda.gov>. After an adequate time period to communicate FDA's decision regarding approval of the CBE-0 labeling supplements and to facilitate submission of conforming CBE-0 supplements by other application holders, as appropriate, the original entry on FDA's Web page would be archived. Approved labeling would continue to be available at <http://labels.fda.gov>. As discussed in section II.B, a prior approval supplement or CBE-0 supplement submitted by an ANDA holder will be approved upon the approval of the same safety-related labeling change for the RLD approved in an NDA under

section 505(c) of the FD&C Act, except that if approval of the NDA for the RLD has been withdrawn under § 314.150, FDA may approve an ANDA holder's prior approval supplement or CBE-0 supplement (see section 505(j)(2)(A)(v) of the FD&C Act and proposed § 314.97(b); see also section II.A.1.b and d). Upon FDA approval of revised labeling, other ANDA holders will be required to submit a CBE-0 supplement with conforming revisions. We invite comment on this approach.

Proposed §§ 314.70(c)(8) and 601.12(f)(2)(iii) state that FDA will promptly post on its Web site information regarding labeling changes proposed in a CBE-0 supplement to an NDA, ANDA, or BLA. This proposal is intended to enhance transparency and facilitate access by health care providers and the public to labeling containing newly acquired information about important drug safety issues so that such information may be used to inform treatment decisions. We also invite comment on whether the benefits of a dedicated FDA Web page for CBE-0 supplements could be realized through modification of FDA's existing online labeling repository (<http://labels.fda.gov>). For example, the online labeling repository could be modified to enable a separate listing of pending CBE-0 supplements, thereby improving existing resources and consolidating labeling information on a single FDA Web page.

Current §§ 314.70(c)(6) and 601.12(f)(2) state that the application holder may distribute the drug accompanied by the revised labeling upon submission to FDA of a CBE-0 supplement. However, FDA expects that if an application holder acquires important new safety-related information that warrants submission of a CBE-0 supplement under §§ 314.70(c)(6) or 601.12(f)(2), the application holder will use available means (e.g., distribution of revised labeling in electronic format to the public) to distribute the revised labeling at the time of submission of the CBE-0 supplement to FDA (compare section II.A.1.d). Indeed, the need to promptly communicate certain safety-related labeling changes based on newly acquired information is the basis for this exception to the general requirement for FDA approval of revised labeling prior to distribution (see section I.B). Accordingly, we are proposing to expressly require that applicants submit final printed labeling in structured product labeling (SPL) format at the time of submission of the CBE-0 supplement so that the revised labeling can be made publicly available on FDA's Web site and in other databases (e.g., DailyMed, a Web site provided by the National Library of Medicine that includes drug labeling submitted to FDA) promptly after submission. This proposed change would make the regulations consistent with FDA's previous announcement that “the Agency will make the revised labeling proposed in a CBE supplement publicly available on its Web site and through the DailyMed shortly after the CBE supplement is received and before FDA has necessarily reviewed or approved it” (draft guidance for industry on “Public Availability of Labeling Changes in 'Changes Being Effected' Supplements” (2006)).¹²¹ We note that the technical means by which the CBE-0 supplements are made publicly available through the FDA Web site may change with evolving technology and Agency practices.

Proposed §§ 314.70(c)(8) and 601.12(f)(2)(iii) would require the applicant to verify that the correct information regarding the labeling changes proposed in its CBE-0 supplement appears on FDA's Web page. If the information is incorrect, then the applicant must contact FDA within 5 business days of posting on the FDA Web page. The applicant may determine that information regarding the labeling changes proposed in its CBE-0 supplement has been posted on the FDA Web page by monitoring the FDA Web page after submission of a CBE-0 supplement or

subscribing to FDA's Web page to receive an email notification. FDA intends to identify the FDA contact person(s) who should receive any corrections to such information for NDAs, ANDAs, and BLAs on the proposed FDA Web page. We invite comment on whether this is a sufficient amount of time for an applicant to check the accuracy and completeness of the posted information regarding the CBE-0 supplement and the link to current labeling.

a. *Contents of supplement.* We are proposing to add § 314.70(c)(8)(i) to clarify FDA's expectations regarding the contents of a CBE-0 supplement submitted under § 314.70(c)(6)(iii), and to facilitate publication of information regarding the CBE-0 supplement on FDA's Web page. Current § 314.70(c)(4) requires that a CBE supplement include information listed in § 314.70(b)(3)(i) through (b)(3)(vii), which describes information that must be included in a CBE supplement for a manufacturing change. To clarify FDA's expectations for the contents of a CBE-0 labeling supplement and to facilitate listing information on FDA's proposed Web page, we are proposing to require that a CBE-0 supplement submitted under § 314.70(c)(6)(iii) contain the following information:

i. *The application number(s) of the drug product(s) involved.* If a CBE-0 supplement is being submitted by an NDA or ANDA holder to multiple applications for a drug product or product class, the application holder should identify the application number of each application to which the CBE-0 supplement is being submitted.

ii. *A description of the labeling change proposed in the CBE-0 supplement.* The applicant should submit a proposed narrative description of the proposed labeling change in the CBE-0 supplement for posting on the FDA Web page. This brief narrative description should include the affected section(s) of labeling, the labeling change, and the source of the data (e.g., spontaneous adverse event reports, published literature, clinical trial, epidemiologic study). For example, "Revised contraindication: Drug X is contraindicated in patients with diabetes. Source: Published literature, epidemiologic study."

iii. *The basis for the labeling change proposed in the CBE-0 supplement.* The basis for the labeling change proposed in the CBE-0 supplement should include available data supporting the change (e.g., spontaneous adverse event reports, published literature, clinical trial, epidemiologic study). If the supplement has been submitted in response to FDA's specific request to submit a CBE-0 supplement for the labeling change (see § 314.70(c)(6)(iii)(E)), the applicant should describe the specific change requested by FDA and reference the FDA communication containing the request.

iv. *A copy of the product labeling proposed in the CBE-0 supplement.* A copy of the final printed labeling containing the changes being effected should be provided in SPL format for posting on FDA's Web site and distribution to DailyMed. The application holder also should submit a copy of the current product labeling annotated with the labeling change proposed in the CBE-0 supplement (e.g., use of underscoring and/or strikethrough text to show the changes being effected in the product labeling proposed in the CBE-0 supplement as compared to the approved labeling).

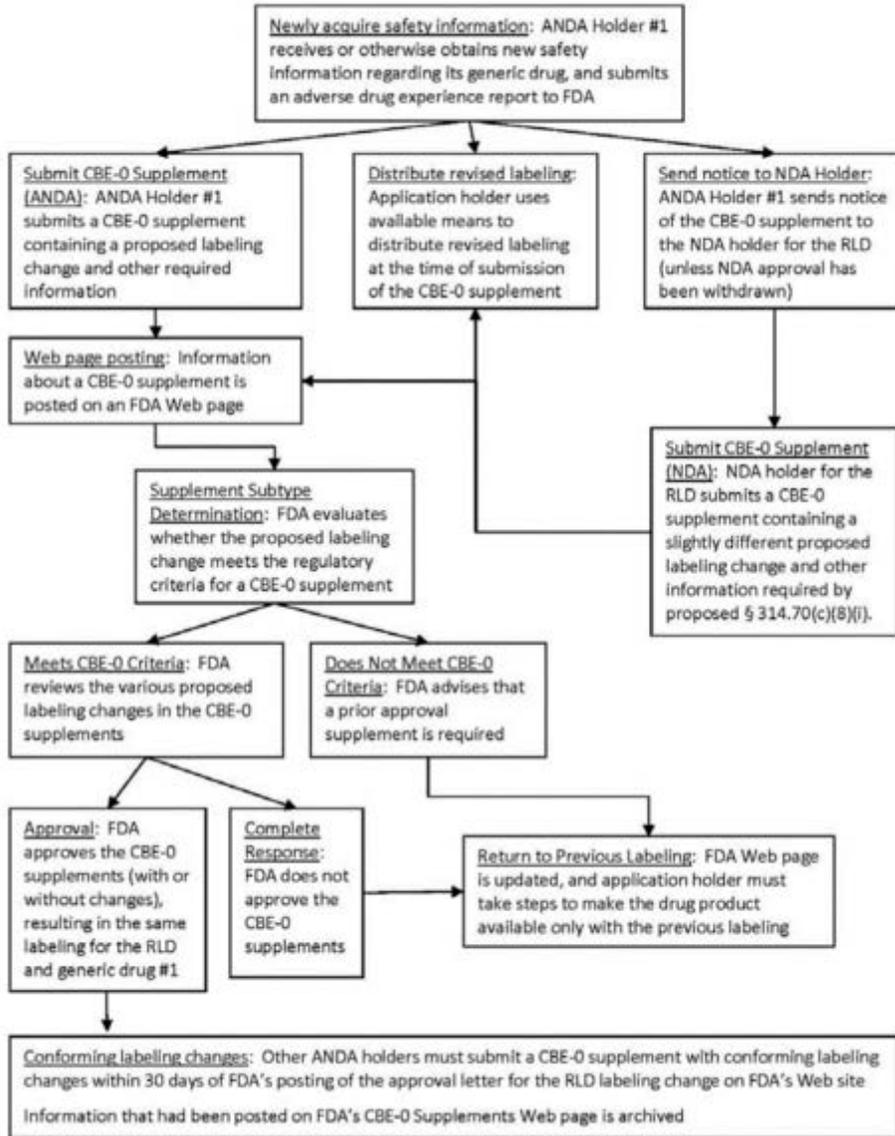
v. *Confirmation that notice has been sent to the NDA holder for the RLD.* If the changes being effected supplement is submitted by an ANDA holder and approval of the NDA for the RLD has not been withdrawn under § 314.150, the ANDA holder must include in its submission a statement confirming that the notice described in proposed § 314.70(c)(8)(ii) has been sent to the NDA holder for the RLD.

b. *Notice of labeling changes being effected.* We are proposing to add § 314.70(c)(8)(ii) to require an ANDA holder to send notice of the labeling change proposed in the CBE-0 supplement, including a copy of the information supporting the change (with any personally identifiable information redacted), to the NDA holder for the RLD at the same time that the supplement to the ANDA is submitted to FDA, unless approval of the NDA has been withdrawn under § 314.150. This proposal would ensure that the NDA holder for the RLD is promptly advised of the newly acquired information that was considered to warrant the labeling change proposed for the drug in the CBE-0 supplement.

The ANDA holder would be required to send a copy of the information (e.g., published literature, spontaneous adverse event reports) supporting the labeling change described in the CBE-0 supplement to the NDA holder for the RLD so that the NDA holder may consider this information as part of its review and evaluation of postmarketing data under § 314.80(b). If the information supporting the ANDA holder's labeling change described in the CBE-0 supplement contains personally identifiable information (e.g., spontaneous adverse event reports), the ANDA holder should redact that information prior to sending a copy of the information to the NDA holder for the RLD, in accordance with [21 CFR 20.63\(f\)](#). The NDA holder has full access to the data upon which the RLD was approved and, in most cases, has substantial knowledge about the postmarketing experience for the drug product. FDA's analysis of whether the labeling change proposed by an ANDA holder in a CBE-0 supplement should be approved (and required for inclusion in the labeling of all versions of the drug) would benefit from the views of the NDA holder for the listed drug that was the basis for ANDA submission. Other holders of NDAs or ANDAs for drug products containing the same active ingredient may learn of pending CBE-0 supplements by subscribing to FDA's proposed Web page, and also may submit CBE-0 supplements or provide comments to FDA regarding a pending CBE-0 supplement. This approach to considering information from other application holders is intended to mitigate concerns that a single ANDA holder may not possess sufficient data to perform an adequate assessment of the potential new safety concern raised by the newly acquired information.

It should be emphasized that interpretation of postmarketing safety data is complex, involving analysis of postapproval clinical data, detailed review of adverse drug experience reports in the context of relevant clinical studies, estimates of drug usage and adverse drug experience reporting rates, estimates of background rates of the adverse event, and other relevant information. FDA recognizes that decisions about how to address a safety concern often are a matter of judgment, about which reasonable persons with relevant expertise may disagree, and this may be reflected in different approaches to proposed labeling changes based on newly acquired safety information (see Guidance on “Drug Safety Information—FDA's Communication to the Public” (2007)). Figure 1 illustrates one of the possible scenarios involving submission of CBE-0 supplements by multiple application holders.

Figure 1. Example of Process for Submission of CBE-0 Supplements by ANDA Holder and NDA Holder



Proposed § 314.70(c)(8)(ii) would provide that an NDA holder or any ANDA holder may submit (on its own initiative or in response to a request from FDA) a labeling supplement or correspondence to its NDA or ANDA, as applicable, regarding the labeling changes proposed in a CBE-0 supplement. It is expected that a valid safety concern regarding a generic drug product also would generally warrant a change to the labeling through a CBE-0 supplement by the NDA holder for the RLD and, as a consequence, other generic drug products that reference the RLD. In the event that the NDA holder for the RLD does not submit a supplement seeking approval for a related or conforming labeling change, FDA may send a supplement request letter to the NDA holder or, if appropriate, notify the responsible person of new safety information under section

505(o)(4) of the FD Act (see [21 U.S.C. 355](#)(o)(2)(A) defining “responsible person”). In situations in which the safety information prompting the submission of the CBE-0 supplement would require a label change for other drugs containing the same active ingredient, even if approved under a different NDA, FDA also may send a supplement request letter to the persons responsible for those other drugs.

We recognize that the authority to order safety labeling changes under section 505(o)(4) of the FD Act for new safety information about a risk of a serious adverse drug experience will not apply to all potential safety-related labeling changes (see [21 U.S.C. 355](#)-1(b) defining “new safety information” and “serious adverse drug experience”). Based on our experience, we expect that NDA holders will implement safety-related labeling changes requested by FDA even if not required under section 505(o)(4) of the FD Act. In circumstances in which section 505(o)(4) of the FD Act does not apply, if the NDA holder declined to submit a supplement to make the change that FDA has concluded is appropriate, FDA would consider whether the NDA holder's failure to update its labeling would warrant the initiation of proceedings to withdraw approval of the NDA (see section 505(e) of the FD&C Act).

It should be noted that if an NDA holder has discontinued marketing a drug product, but approval of the NDA has not been withdrawn under § 314.150, the NDA holder still must comply with applicable statutory and regulatory requirements. These requirements include, for example, postmarketing reporting of adverse drug experiences, submission of an annual report (including a brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product, and a description of actions the applicant has taken or intends to take as a result of this new information) and, if appropriate, proposed revisions to product labeling. If approval of the NDA for the RLD is withdrawn under § 314.150 for reasons other than safety or effectiveness, any generic versions that remain on the market will be expected to contain the same essential labeling.

c. Distribution of revised labeling. We are proposing to add § 314.70(c)(8)(iii) and revise § 601.12(f)(2)(ii) to expressly describe our longstanding practice with respect to labeling supplements that have been submitted as CBE-0 supplements, but that do not meet the regulatory criteria for CBE-0 supplements, and thus do not fall within this narrow exception to the general requirement for FDA approval of revised labeling prior to distribution. Proposed §§ 314.70(c)(8)(iii) and 601.12(f)(2)(ii) explain that if FDA determines during its review period that the supplement does not meet the criteria described in § 314.70(c)(6)(iii) or § 601.12(f)(2)(i), as applicable, the supplement will be converted to a prior approval supplement, and the manufacturer must cease distribution of the drug product(s) accompanied by the revised labeling. In this scenario, the manufacturer must take steps to make the drug product available only with the previous version of the label. This may include, for example, replacing the CBE-0 labeling with the previous labeling on the manufacturer's Web site, requesting replacement of the CBE-0 labeling with the previous labeling on <http://labels.fda.gov>, and attaching the previous package insert to the drug product as soon as feasible thereafter or at the time of next printing of the product labeling for packaging.

This approach is consistent with our clarifying revision in proposed § 314.70(c)(7), which explains that if the Agency does not approve the supplemental application, the manufacturer

must cease distribution of the drug product(s) accompanied by the revised labeling. The current text of § 314.70(c)(7) describes the implications of a complete response letter to the applicant for a CBE supplement for manufacturing changes, and does not expressly address CBE-0 labeling supplements. For consistency with § 314.110 ([21 CFR 314.110](#)), we are proposing to replace the word “disapproves” in § 314.70(c)(7) with the phrase “issues a complete response letter” and to make other editorial changes for clarity.

d. *Conforming labeling requirements.* Proposed § 314.70(c)(8)(iv) would establish a 30-day timeframe in which ANDA holders are required to submit a CBE-0 supplement under § 314.70(c)(6)(iii)(E) with conforming labeling after FDA approval of a revision to the labeling for the RLD. Currently, FDA advises ANDA holders to revise product labeling to conform to the labeling of the RLD “at the very earliest time possible” (see guidance for industry on “Revising ANDA Labeling Following Revision of the RLD Labeling” (2000)). In light of the range of timeframes in which ANDA holders currently submit such labeling supplements, we are proposing to revise these regulations to clarify FDA's expectations regarding the timeframe for submission of conforming labeling changes.

Proposed § 314.70(c)(8)(iv) states that upon FDA approval of changes to the labeling of the RLD, or if approval of the NDA for the RLD has been withdrawn under § 314.150, upon FDA approval of changes to the labeling of an ANDA that relied on the RLD, any other ANDA holder that relied upon the RLD must submit a CBE-0 supplement with conforming labeling revisions within 30 days of FDA's posting of the approval letter for the labeling change on FDA's Web site, unless FDA requires the ANDA holder's labeling revisions at a different time in accordance with sections 505(o)(4) or 505-1 of the FD&C Act, or other applicable authority. The ANDA holder would be expected to submit updated labeling for posting on <http://labels.fda.gov> and DailyMed at the time of submission of the CBE-0 supplement. However, we recognize that distribution of drug products accompanied by an updated package insert may take additional time, depending on how often the drug is packaged, the size of manufacturer inventories, and other factors. Accordingly, proposed § 314.70(c)(8)(iv) is directed to prompt distribution of revised labeling in electronic format, and timely distribution of drug product accompanied by an updated package insert as soon as feasible thereafter or at the time of next printing of the product labeling for packaging.

FDA may require an ANDA holder to submit revised product labeling at a different time for safety labeling changes required under section 505(o)(4) of the FD&C Act or for REMS under section 505-1 of the FD&C Act. This may occur, for example, in the context of approval of modifications to a single, shared system REMS that are made to conform to safety labeling changes (see section 505-1(i)(1)(B) of the FD&C Act).

2. Changes to Highlights of Prescribing Information (Proposed §§ 314.70(c)(6) and 601.12(f)(1) and (f)(2))

We are proposing to revise §§ 314.70(c)(6) and 601.12(f)(1) and (f)(2) to remove the limitation on submission of CBE-0 supplements for changes to the Highlights of drug labeling in the PLR format.

Current §§ 314.70(c)(6) and 601.12(f)(1) and (f)(2) exclude most changes to the information required in the Highlights, which are classified as a “major change” that must be made by a prior approval supplement, unless FDA specifically requests that the labeling change be submitted in a CBE-0 supplement or FDA grants a waiver request under § 314.90. This exception reflected the Agency's earlier view that FDA review and approval of most proposed changes to the information in the Highlights of labeling was necessary because of the difficulty involved in summarizing the complex information presented in the full prescribing information (see “Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products,” [71 FR 3922](#) at 3932, January 24, 2006).

Based on our experience implementing the PLR, we have found this restriction on CBE-0 supplements to be unnecessary in practice. In response to an applicant's inquiry about submission of a CBE-0 supplement for a change that would affect the Highlights of drug labeling, FDA typically waives this limitation under § 314.90 or specifically requests that the applicant proceed with a CBE-0 supplement under § 314.70(c)(6)(iii)(E) or § 601.12(f)(2)(i)(E).

The Highlights of drug labeling is intended to summarize the information that is most important for prescribing the drug safely and effectively. The types of newly acquired information that would otherwise meet the criteria for submission of a CBE-0 supplement include the critical safety information that is presented in the Highlights. Accordingly, we believe that limiting the availability of CBE-0 supplements for changes to the Highlights of drug labeling in the PLR format may pose an unnecessary impediment to prompt communication of the most important safety-related labeling changes (e.g., boxed warnings and contraindications). Compare 50 FR 7452 at 7470, February 22, 1985 (stating that substantive changes in labeling are appropriately approved by FDA in advance, “unless they relate to important safety information, like a new contraindication or warning, that should be immediately conveyed to the user”).

Our proposal to remove the limitation on submission of CBE-0 supplements for changes to the Highlights also would create parity between application holders for drugs with labeling in the older format and application holders for drugs with PLR labeling. For example, this proposal would eliminate differences in the ability of application holders to submit CBE-0 supplements for a new or substantively revised contraindication based solely on whether current labeling appeared in the older format or PLR format.

We also are proposing to make conforming revisions to § 314.70(b)(2)(v)(C) to clarify that a prior approval supplement is required for any changes to the Highlights of drug labeling other than changes under § 314.70(c)(6)(iii), except for the specified changes that may be reported in an annual report.

3. Clarifying Revisions and Editorial Changes

We are proposing to revise the title to § 314.70(c) to refer to CBE-0 supplements to clarify the scope of paragraph (c). As revised, § 314.70(c) would describe changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (CBE-30 supplements) and certain changes being effected pending supplement approval (CBE-0

supplements). We also are proposing to add titles to paragraphs (c)(1) through (c)(7) of § 314.70 for clarity.

We are proposing to revise § 314.70(c)(1) to clarify that submission of a CBE-0 supplement is required for any change in the labeling to reflect newly acquired information of the type described in § 314.70(c)(6)(iii). The current text of § 314.70(c)(1) is directed only to submission of supplements for certain manufacturing changes and does not fully describe the range of supplements for moderate changes that are described by this paragraph.

We are proposing to move the statement regarding the contents of a CBE supplement for certain manufacturing changes from existing § 314.70(c)(4) to § 314.70(c)(3) without changes.

We are proposing to revise § 314.70(c)(6)(iii) to clarify that an NDA holder or ANDA holder may distribute the drug product with revised labeling upon “submission” to FDA of the CBE-0 supplement for the labeling change, rather than upon FDA’s “receipt” of the change. For ANDAs, section 744B(a)(5) of the FD Act ([21 U.S.C. 379j-42\(a\)\(5\)](#)) clarifies the time when a supplement is “submitted” to FDA, whereas the term “received” has a specific meaning that generally refers to FDA’s determination that a submitted application has met certain criteria for completeness (see [21 CFR 314.101](#)). This proposed revision is intended to avoid potential confusion, and more clearly establish the date on which distribution of revised labeling may occur.

B. Approval of Supplements to an Approved ANDA for a Labeling Change (Proposed § 314.97(b))

We are proposing to revise § 314.97 by designating the current text as paragraph (a) and by adding proposed paragraph (b) to clarify the process for approval of a supplement to an approved ANDA for a labeling change. Proposed § 314.97(b) explains that a supplement to an approved ANDA for a safety-related labeling change that is submitted in a prior approval supplement under § 314.70(b) or in a CBE-0 supplement under § 314.70(c)(6) will be approved upon approval of the same labeling change for the RLD, except that if approval of the NDA for the RLD has been withdrawn under § 314.150, FDA may approve an ANDA holder’s prior approval supplement or CBE-0 supplement.

It has been FDA’s longstanding position that an ANDA holder may submit a prior approval supplement to request a change to product labeling, and “FDA will determine whether the labeling for the generic and [reference] listed drugs should be revised” (57 FR 17950 at 17961, April 28, 1992; see also 57 FR 17950 at 17965 (describing requirement for “ANDA applicants to submit a periodic report of adverse drug experiences even if the ANDA applicant has not received any adverse drug experience reports *or initiated any labeling changes*”) (emphasis added)). Proposed § 314.97(b) would expressly state that a prior approval supplement to an ANDA for a safety-related change in product labeling will be approved upon approval of the same labeling for the RLD. This approach ensures that the approved labeling for a generic drug continues to be the same as the approved labeling of its RLD (see section 505(j)(2)(A)(v) of the FD&C Act). If approval of the NDA for the RLD has been withdrawn under § 314.150, FDA

may approve an ANDA holder's prior approval supplement for a safety-related labeling change (see § 314.105; see also proposed § 314.70(c)(8)(iv)).

Similarly, FDA would approve a CBE-0 labeling supplement to an ANDA upon the approval of the same labeling change for the RLD (see section 505(j)(2)(A)(v) of the FD&C Act), except that if approval of the NDA for the RLD has been withdrawn under § 314.150, FDA may approve an ANDA holder's CBE-0 supplement (see § 314.105; see also proposed § 314.70(c)(8)(iv)). As explained in section I.B, FDA may accept, reject, or request modifications to the labeling changes proposed in the CBE-0 supplement. FDA's evaluation of the labeling change proposed by the ANDA holder would consider any submissions related to the proposed labeling change from the NDA holder for the RLD and from any other NDA or ANDA holders for drug products containing the same active ingredient. The Agency intends to act expeditiously, taking into account the reliability of the data, the magnitude and seriousness of the risk, and number of CBE-0 supplements, and reach a decision on the approvability of labeling proposed by ANDA and NDA holders regarding the safety issue at the same time. After approval of a labeling change, other ANDA holders would be required to submit any necessary conforming labeling changes in accordance with proposed § 314.70(c)(8)(iv).

C. Exception for ANDA Labeling Differences Resulting From “Changes Being Effected” Supplement (Proposed § 314.150(b)(10)(iii))

We are proposing to revise § 314.150(b)(10) to provide an additional exception regarding circumstances in which FDA may seek to withdraw approval of an ANDA based on generic drug labeling that is no longer consistent with the labeling for the RLD. Proposed § 314.150(b)(10)(iii) would include, as a permissible difference, changes to generic drug labeling under a CBE-0 supplement, with the understanding that such differences generally will be temporary.

This proposed exception reflects the Agency's judgment that concerns related to temporary differences in labeling between generic drugs and their RLDs are outweighed by the benefit to the public health that would result from all application holders having the ability to independently update drug product labeling to reflect newly acquired information regarding important drug safety issues through CBE-0 labeling supplements (compare section 505(j)(10) of the FD&C Act).

III. Legal Authority

FDA's legal authority to modify §§ 314.70, 314.97, 314.150, and 601.12 arises from the same authority under which FDA initially issued these regulations. The FD Act ([21 U.S.C. 301](#) et seq.) and the PHS Act ([42 U.S.C. 201](#) et seq.) provide FDA with authority over the labeling for drugs and biological products, and authorize the Agency to enact regulations to facilitate FDA's review and approval of applications regarding the labeling for those products. Section 502 of the FD Act ([21 U.S.C. 352](#)) provides that a drug or biological product will be considered misbranded if, among other things, the labeling for the product is false or misleading in any particular ([21 U.S.C. 352\(a\)](#); see also [42 U.S.C. 262\(j\)](#)). Under section 502(f) of the FD Act, a product is misbranded unless its labeling bears adequate directions for use, including adequate warnings

against, among other things, unsafe dosage or methods or duration of administration or application. Moreover, under section 502(j) of the FD Act, a product is misbranded if it is dangerous to health when used in the manner prescribed, recommended, or suggested in its labeling.

In addition to the misbranding provisions, the premarket approval provisions of the FD Act authorize FDA to require that product labeling provide adequate information to permit safe and effective use of the product. Under section 505(c) of the FD Act ([21 U.S.C. 355](#)), FDA will approve an NDA only if the drug is shown to be both safe and effective for its intended use under the conditions set forth in the drug's labeling. Under section 505(j) of the FD Act, FDA will approve an ANDA only if the drug is, with limited exceptions, the same as a drug previously approved under section 505(c) of the FD Act with respect to active ingredient(s), dosage form, route of administration, strength, labeling, and conditions of use, among other characteristics, and is bioequivalent to the RLD.

Section 351 of the PHS Act ([42 U.S.C. 262](#)) provides additional legal authority for the Agency to regulate the labeling of biological products. Licenses for biological products are to be issued only upon a showing that the biological product is safe, pure, and potent ([42 U.S.C. 262\(a\)](#)). Section 351(b) of the PHS Act prohibits any person from falsely labeling any package or container of a biological product. FDA's regulations in [21 CFR part 201](#) apply to all prescription drug products, including biological products.

In addition, section 701(a) of the FD Act ([21 U.S.C. 371\(a\)](#)) authorizes FDA to issue regulations for the efficient enforcement of the FD Act. FDA's regulations relating to CBE-0 supplements are supported by this provision. In 1965, FDA determined that, in the interest of drug safety, manufacturers should make certain safety-related changes to their product labeling at the earliest possible time (see 30 FR 993, January 30, 1965). Thus, for nearly 50 years, FDA, as the Agency entrusted with administration and enforcement of the FD Act and the protection and promotion of the public health, has required NDA holders, and subsequently BLA holders, to update drug product labeling with important, newly acquired safety information through submission of a CBE-0 supplement.

FDA's authority to extend the CBE-0 supplement process for safety-related labeling changes to ANDA holders arises from the same authority under which our regulations relating to NDA holders and BLA holders were issued. Nothing in the Hatch-Waxman Amendments or subsequent amendments to the FD&C Act limits the Agency's authority to revise the CBE-0 supplement regulations to apply to ANDA holders to help ensure that generic drugs remain safe and effective under the conditions of use prescribed, recommended, or suggested in the labeling throughout the life cycle of the generic drug product.

In *Pliva v. Mensing*, the Supreme Court recognized that “Congress and the FDA retain the authority to change the law and regulations if they so desire” (131 S. Ct. 2567, 2582). Recently, in *Mutual Pharmaceutical Co., Inc. v. Bartlett*, 133 S. Ct. 2466 (2013), the Court indicated that “Congress' decision to regulate the manufacture and sale of generic drugs in a way that reduces their cost to patients but leaves generic drug manufacturers incapable of modifying either the drugs' compositions or their warnings” contributed to the outcome in that case (preemption of the

tort claim against the generic manufacturer). We do not read this language to suggest that the Agency would not have authority to extend the CBE-0 supplement process to ANDA holders. The changes proposed in this rulemaking are authorized under the FD&C Act, which provides authority for FDA to permit NDA holders and BLA holders to change their product labeling to include certain newly acquired safety-related information through submission of a CBE-0 supplement.

IV. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, [Executive Order 13563](#), the Regulatory Flexibility Act ([5 U.S.C. 601-612](#)), and the Unfunded Mandates Reform Act of 1995 (Pub. L.104-4). Executive Orders 12866 and 13563 direct Agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Agency believes that this proposed rule would not be an economically significant regulatory action as defined by Executive Order 12866.

If a rule has a significant economic impact on a substantial number of small businesses, the Regulatory Flexibility Act requires Agencies to analyze regulatory alternatives that would minimize any significant impact of a rule on small entities. FDA has determined that this proposed rule would not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$141 million, using the most current (2012) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

The public health benefits from adoption of the proposed rule are not quantified. By allowing all application holders to update labeling based on newly acquired information that meets the criteria for a CBE-0 supplement, communication of important drug safety information to prescribing health care providers and the public could be improved. The proposed rule may reduce the time in which ANDA holders make safety-related labeling changes for generic drugs for which approval of the NDA for the RLD has been withdrawn. In addition, the proposed rule generally would reduce the time in which all ANDA holders make safety-related labeling changes, by requiring such ANDA holders to submit conforming labeling changes within 30 days of FDA's posting of the approval letter for the RLD's labeling change on its Web site. The primary estimate of the costs of the proposed rule includes costs to ANDA and NDA holders for submitting and reviewing CBE-0 supplements. We assume that the proposed rule will have no effect on the number of CBE-0 supplements submitted by BLA holders.

The proposed rule is expected to generate little cost. The Agency estimates the net annual social costs to be between \$4,237 and \$25,852. The present discounted value over 20 years would be in the range of \$63,040 to \$384,616 at a 3 percent discount rate, and in the range of \$44,890 to \$273,879 at a 7 percent discount rate.

FDA has examined the economic implications of the final rule as required by the Regulatory Flexibility Act. This proposed rule would only impose new burdens on small generic drug manufacturers who submit CBE-0 supplements for safety-related labeling changes. Given the small cost per submission and the uncertainty in the estimated number of CBE-0 labeling supplements for safety-related labeling changes that may be submitted by an ANDA holder, we do not expect this proposed rule to impose a significant impact on a substantial number of small entities. We therefore propose to certify that that this proposed rule would not have a significant economic impact on a substantial number of small entities.

V. Paperwork Reduction Act of 1995

This proposed rule contains collections of information that are subject to review by the Office of Management and Budget (OMB) under the PRA ([44 U.S.C. 3501-3520](#)). A description of these provisions is given in this document with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

FDA invites comments on these topics: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products

Description: The proposed rule would permit ANDA holders to submit a CBE-0 supplement for certain types of labeling changes based on newly acquired information. At the time of submission, the ANDA holder would be required to send notice of the labeling change proposed in the CBE-0 supplement, including a copy of the information supporting the change, to the NDA holder for the RLD, unless the NDA for the RLD has been withdrawn.

Description of Respondents: Respondents to this collection of information are NDA holders, ANDA holders, and BLA holders.

Burden Estimates: FDA regulations at §§ 314.70 and 314.97 set forth the requirements for submitting supplements to FDA for certain changes to an approved NDA or ANDA. These regulations specify the submission of supplements at different times, depending on the change to

the approved application. Under § 314.70(c)(6), an applicant may commence distribution of a drug product upon receipt by FDA of a supplement for a change to the applicant's approved application (a CBE-0 supplement). The changes for which a CBE-0 supplement may be submitted include, among other things, changes in the labeling (§ 314.70(c)(6)(iii)) to reflect newly acquired information, for example, to add or strengthen a contraindication, warning, precaution, or adverse reaction for which there is reasonable evidence of a causal association.

FDA currently has OMB approval (OMB control number 0910-0001) for the submission of supplements to FDA for changes to an approved NDA or ANDA under §§ 314.70 (including § 314.70(c)(6)(iii)) and 314.97.

Under the proposed rule, ANDA holders would be permitted to submit a supplement to FDA for certain types of labeling changes based on newly acquired information. This collection of information is not currently approved under OMB control number [0910-0001](#). Under proposed § 314.70(c)(8), if an NDA holder or ANDA holder obtains or otherwise receives newly acquired information that should be reflected in product labeling to accomplish any of the objectives specifically described in § 314.70(c)(6)(iii), the NDA holder or ANDA holder should submit a CBE-0 supplement to FDA. Proposed § 314.70(c)(8) is intended to permit ANDA holders to update product labeling promptly, without FDA's special permission and assistance, to reflect newly acquired information that meets the criteria described in § 314.70(c)(6)(iii) irrespective of whether the revised labeling differs from that of the RLD.

To minimize confusion and make safety-related changes to generic drug labeling readily available to prescribing health care providers and the public while FDA is reviewing a CBE-0 supplement, FDA would establish, under proposed § 314.70(c)(8), a dedicated Web page (or, alternatively, a modification of an existing FDA Web page) on which FDA would promptly post information regarding the labeling changes proposed in a CBE-0 supplement. ANDA holders would be required to verify that the correct information regarding the labeling changes proposed in their CBE-0 supplement appears on the FDA Web page. If the information is incorrect, the ANDA holder must contact the appropriate FDA review division within 2 business days of posting on the FDA Web page.

At the time of submission of the CBE-0 labeling supplement to FDA, proposed § 314.70(c)(8)(ii) would require the ANDA holder to send notice of the labeling change proposed in the supplement, including a copy of the information supporting the change, to the NDA holder for the RLD, unless the NDA for the RLD has been withdrawn.

Based on the data summarized in section IV (Analysis of Impacts), we estimate that a total of approximately 15 ANDA holders (“number of respondents” in table 1) would submit to us annually a total of approximately 20 CBE-0 labeling supplements under proposed § 314.70(c)(8), if this rule is finalized (“total annual responses” in table 1). We also estimate that preparing and submitting each CBE-0 labeling supplement under proposed § 314.70(c)(8) will take approximately 12 hours per ANDA holder (“hours per response” in table 1). This burden hour estimate includes the time needed by an ANDA holder to verify, as required under proposed § 314.70(c)(8), that the correct information regarding the labeling change proposed in its CBE-0

supplement appears on the FDA Web page, and the time needed to contact FDA if the information is incorrect.

In addition, we estimate that a total of approximately 15 ANDA holders would send notice of the labeling change proposed in each of the 20 CBE-0 labeling supplements, including a copy of the information supporting the change, to the NDA holder for the RLD, as required under proposed § 314.70(c)(8)(ii). We also estimate that preparing and sending each notice would take approximately 3 hours per ANDA holder.

FDA estimates the burden of this collection of information as follows:

Table 1—Estimated Annual Reporting Burden¹ [Back to Top](#)

21 CFR Section	Number of respondents	Number of responses per respondent	Total annual responses	Hours per response	Total hours
CBE-0 supplement submission by ANDA holders (314.70(c)(8))	15	1.34	20	12	240
ANDA holder notice to NDA holder (314.70(c)(8)(ii))	15	1.34	20	3	60
Total					300

¹There are no capital costs or operating and maintenance costs associated with this collection of information.

To ensure that comments on the information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, FAX: 202-395-7245, or emailed to oir_submission@omb.eop.gov. All comments should be identified with the title, “Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products.”

In compliance with the PRA (44 U.S.C. 3407(d)), the Agency has submitted the information collection provisions of this proposed rule to OMB for review. These requirements will not be effective until FDA obtains OMB approval. FDA will publish a notice concerning OMB approval of these requirements in the Federal Register.

VI. Environmental Impact [Back to Top](#)

The Agency has determined under [21 CFR 25.30](#)(h) and 25.31(a) and (g) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Effective Date [Back to Top](#)

FDA proposes that any final rule based on this proposal become effective 30 days after the date of its publication in the Federal Register.

We intend to apply this rule, if finalized, to any submission received by FDA on or after the effective date. This proposed rule provides sufficient notice to all interested parties, including NDA holders, ANDA holders, and BLA holders, to adjust their submissions and actions by the time we issue any final rule. However, we invite comments on how a final rule should be implemented.

VIII. Federalism [Back to Top](#)

FDA has analyzed this proposed rule in accordance with the principles set forth in [Executive Order 13132](#). FDA has determined that the proposed rule, if finalized, would not contain policies that would have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the Agency tentatively concludes that the proposed rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

IX. Request for Comments [Back to Top](#)

Interested persons may submit either electronic comments regarding this document to <http://www.regulations.gov> or written comments to the Division of Dockets Management (see ADDRESSES). It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

X. References [Back to Top](#)

The following references have been placed on display in the Division of Dockets Management (see ADDRESSES) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at <http://www.regulations.gov>. (FDA has verified the Web site address in this reference section, but we are not responsible for any subsequent changes to the Web site after this document publishes in the Federal Register.)

1. IMS Institute for Healthcare Informatics, “The Use of Medicines in the United States: Review of 2011,” April 2012 (available at http://www.imshealth.com/ims/Global/Content/Insights/IMS%20Institute%20for%20Healthcare%20Informatics/IHII_Medicines_in_U.S_Report_2011.pdf).
2. Lester J., G. A. Neyarapally, E. Lipowski, et al., “Evaluation of FDA Safety-Related Drug Label Changes in 2010,” *Pharmacoepidemiology Drug Safety*, vol. 22, pp. 302-305, 2013.

List of Subjects [Back to Top](#)

[21 CFR Part 314](#)

- [Administrative practice and procedure](#)
- [Confidential business information](#)
- [Drugs](#)
- [Reporting and recordkeeping requirements](#)

[21 CFR Part 601](#)

- [Administrative practice and procedure](#)
- [Biologics](#)
- [Confidential business information](#)

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, FDA proposes to amend [21 CFR parts 314](#) and 601 as follows:

begin regulatory text

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

1.The authority citation for [21 CFR part 314](#) continues to read as follows:

Authority:

[21 U.S.C. 321](#), 331, 351, 352, 353, 355, 356, 356a, 356b, 356c, 371, 374, 379e.

§ 314.70 [Amended]

2.Amend § 314.70 as follows:

- Revise paragraph (b)(2)(v)(C) introductory text;
- Revise the paragraph (c) heading;
- Add headings to paragraphs (c)(1) through (c)(7);
- Revise paragraphs (c)(1), (c)(3), (c)(4), (c)(6) introductory text, (c)(6)(iii) introductory text, and (c)(7); and

e. Add new paragraph (c)(8).

§ 314.70 Supplements and other changes to an approved application.

* * * * *

(b) * * *

(2) * * *

(v) * * *

(C) Any change to the information required by § 201.57(a) of this chapter other than changes under paragraph (c)(6)(iii) of this section, with the following exceptions that may be reported in an annual report under paragraph (d)(2)(x) of this section:

* * * * *

(c) Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change and certain changes being effected pending supplement approval (moderate changes).

(1) Types of changes for which a supplement is required. A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. A supplement also must be submitted for any change in the labeling to reflect newly acquired information of the type described in paragraph (c)(6)(iii) of this section. If the supplement provides for a labeling change under paragraph (c)(6)(iii) of this section, 12 copies of the final printed labeling must be included.

(2) Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (changes being effected in 30 days). * * *

* * * * *

(3) Explanation of basis for the change and supplement identifier. A supplement submitted under paragraph (c)(1) of this section is required to give a full explanation of the basis for the change and identify the date on which the change is to be made. The supplement must be labeled “Supplement—Changes Being Effected in 30 Days” or, if applicable under paragraph (c)(6) of this section, “Supplement—Changes Being Effected.” The information listed in paragraphs (b)(3)(i) through (b)(3)(vii) of this section must be contained in the supplement.

(4) *Distribution of drug product pending supplement approval (for changes being effected in 30 days).* Pending approval of the supplement by FDA, except as provided in paragraph (c)(6) of this section, distribution of the drug product made using the change may begin not less than 30 days after receipt of the supplement by FDA.

(5) *Limitations on distribution of drug product pending supplement approval (for changes being effected in 30 days).* * * *

* * * * *

(6) *Changes requiring supplement submission prior to distribution of the drug product made using the change (changes being effected).* The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribution of the drug product involved upon submission to the agency of a supplement for the change. These changes include, but are not limited to:

(i) * * *

(ii) * * *

(iii) Changes in the labeling to reflect newly acquired information to accomplish any of the following:

* * * * *

(7) *Effect of complete response letter for changes being effected supplement.* If the agency issues a complete response letter to the supplemental application, the manufacturer may be ordered to cease distribution of the drug product(s) made with the manufacturing change or, if the supplemental application was submitted for a labeling change under paragraph (c)(6) of this section, the manufacturer must cease distribution of the drug product(s) accompanied by the revised labeling.

(8) *Equal applicability to application holders and abbreviated application holders.* An application holder may submit to its approved application or abbreviated application a supplement described by paragraph (c)(6)(iii) of this section. FDA will promptly post on its Web site information regarding the labeling changes proposed in the changes being effected supplement. The applicant must verify that the correct information regarding the labeling changes proposed in the changes being effected supplement appears on FDA's Web site and must contact FDA within 5 business days of posting if the information is incorrect.

(i) *Contents of supplement.* A supplement to an approved application or abbreviated application described by paragraph (c)(6)(iii) of this section must contain the following information:

(A) The application number(s) of the drug product(s) involved;

(B) A description of the labeling change proposed in the changes being effected supplement;

(C) The basis for the labeling change proposed in the changes being effected supplement, including the data supporting the change or, if submitted under paragraph (c)(6)(iii)(E), the specific change requested by FDA;

(D) A copy of the final printed labeling and current product labeling annotated with the labeling change proposed in the changes being effected supplement;

(E) If the changes being effected supplement is submitted by an abbreviated application holder and approval of the application for the reference listed drug has not been withdrawn under § 314.150 of this chapter, a statement confirming that the notice described in paragraph (c)(8)(ii) of this section has been sent to the application holder for the reference listed drug.

(ii) *Notice of labeling changes being effected.* An abbreviated application holder must send notice of the labeling change proposed in the changes being effected supplement, including a copy of the information supporting the change (with any personally identifiable information redacted), to the application holder for the reference listed drug at the same time that the supplement to the abbreviated application is submitted to FDA, unless approval of the application has been withdrawn under § 314.150 of this chapter. An application holder or any abbreviated application holder may submit (on its own initiative or in response to a request from FDA) a labeling supplement or correspondence to its application or abbreviated application, as applicable, regarding the proposed labeling changes.

(iii) *Distribution of revised labeling.* Pending approval of the supplement by FDA, distribution of the drug product with the revised labeling may be made by an application holder or abbreviated application holder upon submission to FDA of the supplement, except that if FDA determines during its review period that the supplement does not meet the criteria described in paragraph (c)(6)(iii) of this section, the supplement will be converted to a prior approval supplement, and the manufacturer must cease distribution of the drug product(s) accompanied by the revised labeling.

(iv) *Conforming labeling requirements.* Upon FDA approval of changes to the labeling of the reference listed drug or, if the application for the reference listed drug has been withdrawn, upon FDA approval of changes to the labeling of an abbreviated application that relied on the reference listed drug, any other abbreviated application holder that relied upon the reference listed drug must submit a supplement under paragraph (c)(6)(iii)(E) of this section with conforming labeling revisions within 30 days of FDA's posting of the approval letter on its Web site, unless FDA requires the abbreviated application holder's labeling revisions at a different time in accordance with sections 505(o)(4) or 505-1 of the Federal Food, Drug, and Cosmetic Act.

* * * * *

§ 314.97 [Amended]

3.Revise § 314.97 to read as follows:

§ 314.97 Supplements and other changes to an approved abbreviated application.

(a) The applicant must comply with the requirements of §§ 314.70 and 314.71 regarding the submission of supplemental applications and other changes to an approved abbreviated application.

(b) A supplement to an approved abbreviated application for a safety-related change in the labeling that is submitted under § 314.70(b) or (c)(6) will be approved upon approval of the same labeling change for the reference listed drug, except that if approval of the application for the reference listed drug has been withdrawn under § 314.150, FDA may approve such a supplement to an approved abbreviated application.

§ 314.150 [Amended]

4. Amend § 314.150 as follows:

a. In paragraph (b)(10)(i), remove the word “or”;

b. In paragraph (b)(10)(ii), remove the period and replace with a semicolon followed by the word “or”; and

c. Add paragraph (b)(10)(iii).

§ 314.150 Withdrawal of approval of an application or abbreviated application.

* * * * *

(b) * * *

(10) * * *

(iii) Changes to the labeling for the drug product that is the subject of the abbreviated application under § 314.70(c)(6)(iii) of this chapter.

* * * * *

PART 601—LICENSING

5. The authority citation for [21 CFR part 601](#) continues to read as follows:

Authority:

[15 U.S.C. 1451-1561](#); [21 U.S.C. 321](#), 351, 352, 353, 355, 356b, 360, 360c-360f, 360h-360j, 371, 374, 379e, 381; [42 U.S.C. 216](#), 241, 262, 263, 264; sec 122, [Pub. L. 105-115](#), 111 Stat. 2322 ([21 U.S.C. 355](#) note).

6. Amend § 601.12 by revising paragraphs (f)(1), (f)(2)(i) introductory paragraph, and (f)(2)(ii); and by adding new paragraph (f)(2)(iii) to read as follows:

§ 601.12 Changes to an approved application.

* * * * *

(f) * * * (1) *Labeling changes requiring supplement submission—FDA approval must be obtained before distribution of the product with the labeling change.* Except as described in paragraphs (f)(2) and (f)(3) of this section, an applicant shall submit a supplement describing a proposed change in the package insert, package label, container label, or, if applicable, a Medication Guide required under part 208 of this chapter, and include the information necessary to support the proposed change. The supplement shall clearly highlight the proposed change in the labeling. An applicant may report the minor changes to the information specified in paragraph (f)(3)(i)(D) of this section in an annual report. The applicant shall obtain approval from FDA prior to distribution of the product with the labeling change.

(2) *Labeling changes requiring supplement submission—product with a labeling change that may be distributed before FDA approval.* (i) An applicant shall submit, at the time such change is made, a supplement for any change in the package insert, package label, or container label to reflect newly acquired information to accomplish any of the following:

* * * * *

(ii) Pending approval of the supplement by FDA, the applicant may distribute a product with a package insert, package label, or container label bearing such change at the time the supplement is submitted, except that if FDA determines during its review period that the supplement does not meet the criteria described in paragraph (f)(2)(i) of this section, the supplement will be converted to a prior approval supplement, and the manufacturer must cease distribution of the drug product(s) accompanied by the revised labeling. The supplement shall clearly identify the change being made and include necessary supporting data. The supplement and its mailing cover shall be plainly marked: “Special Labeling Supplement—Changes Being Effected.”

(iii) FDA will promptly post on its Web site information regarding the labeling changes proposed in the changes being effected supplement. The applicant must verify that the correct information regarding the labeling changes proposed in the changes being effected supplement appears on FDA's Web site and must contact FDA within 5 business days of posting if the information is incorrect.

* * * * *

end regulatory text

Dated: November 5, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. [2013-26799](#) Filed 11-8-13; 11:15 am]

BILLING CODE 4160-01-P

Footnotes

1. For the purposes of this document, unless otherwise specified, references to “drugs” or “drug products” include drugs approved under the FD Act and biological products licensed under the PHS Act, other than biological products that also meet the definition of a device in section 201(h) of the FD Act ([21 U.S.C. 321\(h\)](#)).
2. When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

Attachment 5



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nabp

.Pharmacy gTLD Program Update for Stakeholders: February 2014

National Association of Boards of Pharmacy® (NABP®) has reached another milestone on its way to becoming the registry operator of the .pharmacy new generic Top-Level Domain (gTLD). The Internet Corporation for Assigned Names and Numbers (ICANN) notified NABP on February 12, 2014, that .pharmacy is now eligible for contracting the first step in the transition to delegation and gTLD launch.

NABP learned on May 16, 2013, that .pharmacy had passed its Initial Evaluation. Since then, NABP has been working to operationalize its plans to launch .pharmacy in line with its core mission of promoting global public health and patient safety, while awaiting ICANN's removal of certain roadblocks that remained in place until this week.

Pending Safeguard Requirements

In April 2013, ICANN instituted a freeze on many applications that it identified as belonging to regulated sectors, including .pharmacy, based on the advice of its Governmental Advisory Committee (GAC). The GAC advised ICANN to require specific safeguards for these gTLDs, leaving it to ICANN to develop and execute a plan to implement these new requirements. Until this advice could be addressed, ICANN instituted a freeze on such applications, preventing NABP and other affected applicants from moving forward with contracting and delegation of their gTLDs.

In late October 2013, the New gTLD Program Committee (NGPC) of the ICANN Board stated its intent to implement the safeguards recommended by the GAC through additional Public Interest Commitments (PICs) to be incorporated into the affected applicants' contracts, or Registry Agreements, with ICANN; at the same time, ICANN communicated an implementation framework that proposed language for these additional PICs, for which it sought approval from the GAC. Following the ICANN Public Meeting in Buenos Aires, the GAC communicated to ICANN that it welcomed the proposed approach for addressing the GAC's recommended safeguards, giving the ICANN Board a green light to approve and implement this framework.

At the February 5 meeting of the NGPC, this implementation framework was officially approved. In the meeting minutes, the NGPC published final language for the additional PICs for applicants in regulated sectors. ICANN has quickly taken action on the NGPC resolution, issuing a notice to NABP on February 12, that it was now eligible to proceed with contracting. It is expected that ICANN will publish more information in the coming days regarding any additional steps that NABP must undertake to incorporate the additional PIC language into its Registry Agreement during the contracting process. Executing a Registry Agreement with ICANN is a major step in moving a new gTLD from concept to Internet.

Essentially, the GAC safeguards obligate registry operators (like NABP) to implement certain contractual requirements by way of ICANN-accredited registrars, to ensure that domain name registrants comply with applicable consumer protection and privacy laws. Given that these safeguards are consistent with NABP's eligibility requirements for .pharmacy domain names, the implementation plans for the GAC advice are very workable solutions from NABP's perspective, and would allow the .pharmacy application to proceed

without any significant impediments to its business plans. Meanwhile, with the green light from ICANN to enter the contracting phase, NABP is undertaking a comprehensive review of its proposed registration policies and working to ensure its full compliance with the PIC in order to align .pharmacy with the GAC safeguards.

Next Steps

Once the Registry Agreement with ICANN has been executed, NABP will work with its back-end registry services provider, Neustar, to conduct Pre-Delegation Testing to demonstrate to ICANN its technical capability to operate the gTLD. Subsequently, .pharmacy will be slotted for delegation into the root by way of the Internet Assigned Numbers Authority. In this process .pharmacy will “go live” and become a viable new namespace, under which .pharmacy domain names can be registered and navigated to by consumers. While, as of third quarter 2013, it had been anticipated that .pharmacy might be ready to launch by April 2014, we are now advised the timeline for launch has been pushed back further due to the delays in ICANN’s processes noted above. The actual launch date remains to be determined and will depend on the speed at which NABP moves through the contracting process.

Pharmacy Community

NABP intends the .pharmacy gTLD to be international in scope, comprising registrants in the following categories both within and outside the United States:

- Independent community pharmacies
- Chain pharmacies and retailers offering pharmacy services
- Pharmacy benefits management companies
- Veterinary pharmacies
- Schools and colleges of pharmacy
- Continuing pharmacy education providers
- Wholesale drug distributors
- Pharmaceutical manufacturers
- Accredited durable medical equipment, prosthetics, orthotics, and supplies providers
- Prescription drug-related patient advocacy and consumer education groups
- Prescription drug information and pharmacy referral sites
- Medical professionals advertising services related to a prescription drug

While registration will be voluntary, .pharmacy domain name holders will be required to adhere to an Authorized Usage Policy (AUP) that will govern how registrants within .pharmacy may use their domain name(s) to ensure they serve the needs of the global .pharmacy community. The timing and phases of international rollout will depend upon the ability to liaise with national standards-setting bodies and licensing bodies that can verify compliance with applicable laws.

Global Partners and Core Standards

Through its VIPPS[®] (Verified Internet Pharmacy Practice Sites^{CM}) accreditation program, NABP has been vetting US-based Internet pharmacies for compliance with US federal and state laws and established practice standards for nearly 15 years. Upon the rollout of .pharmacy, NABP will work with its international partners to uphold core standards that are consistent with the purpose of the .pharmacy gTLD and the mission of promoting the public health. These core standards will complement laws and regulations that are particular to the jurisdiction(s) in which a .pharmacy domain registrant is physically located, ships, dispenses, or sells medications.

NABP will work with members of the global pharmacy community to establish ad-hoc National Standard Setting Committees to provide expertise on matters specific to individual national jurisdictions. The tasks of these committees may include defining national specifications that will be required of registrants in particular jurisdictions, as well as verifying pharmacy licensure and good standing for international and multinational pharmacies and related entities. This will ensure that the benefits of the .pharmacy gTLD will be extended to international and multinational pharmaceutical entities and consumers alike.

Marketing and Communications

The .pharmacy gTLD will provide a powerful tool to educate consumers to distinguish legitimate online pharmacies from the thousands of rogue Internet drug-outlets and will reinforce the value of purchasing medications only from trusted online sources. To help educate the pharmacy community about the .pharmacy gTLD, NABP staff is developing a website to serve as a hub for information about .pharmacy, its purpose, policies, supporters, and registrants – as well as the required directory of all .pharmacy domain name registrants. The site will be launched as *www.dotPharmacy.net* by April 2014. Pending the launch of the .pharmacy gTLD, this content will be migrated to a .pharmacy domain. Currently, this URL redirects to a page providing more information about .pharmacy on the NABP website.

Attachment 6



California State Board of Pharmacy

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www.pharmacy.ca.gov

BUSINESS, CONSUMER SERVICES and HOUSING AGENCY

DEPARTMENT OF CONSUMER AFFAIRS

GOVERNOR EDMUND G. BROWN JR.

PUBLIC SERVICE ANNOUNCEMENT

Prescription Drug Abuse Awareness Month

START DATE: Immediately

Contact: Joyia Emard

(916) 574-7957

Joyia.emard@dca.ca.gov

15 SECONDS

MORE PEOPLE DIE EACH YEAR FROM PRESCRIPTION DRUG OVERDOSES THAN CAR ACCIDENTS. PROTECT

YOUR FAMILY. GET PRESCRIPTION DRUGS OUT OF YOUR MEDICINE CABINET AND LOCK THEM UP.

SAFELY DISPOSE OF UNUSED OR EXPIRED DRUGS. LEARN MORE AT PHARMACY.CA.GOV.

- End -



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PUBLIC SERVICE ANNOUNCEMENT

Prescription Drug Abuse Awareness Month

START DATE: Immediately

Contact: Joyia Emard

(916) 574-7957

Joyia.emard@dca.ca.gov

30 SECONDS

PRESCRIPTION DRUG ABUSE IS A NATIONAL EPIDEMIC AND CAN LEAD TO ADDICTION, OVERDOSE AND DEATH. MANY TEENS GET PRESCRIPTION DRUGS AT HOME FOR FREE AND THINK THEY GIVE A SAFE HIGH. PROTECT YOUR FAMILY. SAFEGUARD YOUR PRESCRIPTION MEDICATIONS. GET THEM OUT OF YOUR MEDICINE CABINET AND LOCK THEM UP. SAFELY DISPOSE OF UNUSED OR EXPIRED DRUGS. SPREAD THE WORD TO FAMILY AND FRIENDS, INCLUDING GRANDPARENTS. LEARN MORE AT PHARMACY.CA.GOV. A MESSAGE FROM THE CALIFORNIA STATE BOARD OF PHARMACY.

- End -



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BUSINESS, CONSUMER SERVICES and HOUSING AGENCY

DEPARTMENT OF CONSUMER AFFAIRS

GOVERNOR EDMUND G. BROWN JR.

PUBLIC SERVICE ANNOUNCEMENT

Prescription Drug Abuse Prevention

START DATE: Immediately

Contact: Joyia Emard

(916) 574-7957

Joyia.emard@dca.ca.gov

60 SECONDS

EACH YEAR, MORE PEOPLE DIE FROM PRESCRIPTION DRUG OVERDOSES THAN FROM CAR ACCIDENTS.

ABUSE OF PRESCRIPTION DRUGS IS A NATIONAL EPIDEMIC AND CAN LEAD TO ADDICTION, OVERDOSE

AND EVEN DEATH. DID YOU KNOW MANY TEENS GET THEIR DRUGS FOR FREE FROM THEIR FAMILY AND

FRIENDS' MEDICINE CABINETS? THEY THINK PRESCRIPTION DRUGS GIVE A SAFE HIGH. PROTECT YOUR

FAMILY AND LOVED ONES. SECURE AND MONITOR PRESCRIPTION DRUGS AND DISPOSE OF UNUSED OR

EXPIRED DRUGS. START BY COUNTING YOUR PILLS, THEN GET THEM OUT OF YOUR EASILY ACCESSIBLE

MEDICINE CABINET AND LOCK THEM UP. KEEP TRACK OF YOUR FAMILY'S REFILLS BECAUSE NEEDING

REFILLS MORE OFTEN THAN EXPECTED COULD INDICATE A PROBLEM. IF YOUR TEEN HAS BEEN

PRESCRIBED A DRUG, CONTROL THE MEDICATION AND MONITOR THE DOSES AND REFILLS. SPREAD THE

WORD TO FAMILY AND FRIENDS, INCLUDING GRANDPARENTS. LEARN MORE AT PHARMACY.CA.GOV.

BROUGHT TO YOU BY THE CALIFORNIA STATE BOARD OF PHARMACY.

- End -

Attachment 7

Patient centered labels help with medication adherence

A 2005 State Senate resolution sought to study the causes of medication errors and make recommendations for changes in the health care system that would reduce errors associated with the delivery of prescription and over-the-counter medication to consumers.

Results from this study prompted the California Legislature in 2007 to enact SB 472, which directed the California State Board of Pharmacy to develop parameters for “patient centered labels.”

This legislation, enacted as Section 4076.5 of the California Business and Professions Code, applies to any prescription medication dispensed to patients in the state.

The law provides that patient-centered labels contain standardized directions for use whenever possible; larger and simpler font types and sizes; and placement of information that considers the needs of patients with limited English proficiency and senior citizens. The labels should feature the information patients or caregivers most often seek out or need in order to understand how to safely taking the medication.

Title 16, California Code of Regulations section 1707.5, establishes specific parameters for patient-centered labels on prescription drug containers and went into effect in January 2011.

The resulting label requirements apply to pharmacies; mail order pharmacies outside of the state that ship to patients in California; and to physicians and other prescribers who dispense medication to patients.

At least fifty percent of the prescription label must include only the following:

- Name of the patient
- Manufacturer’s trade name, or generic name and manufacturer of the drug and strength of the drug.
- Directions for use of the drug
- Condition or purpose for which the drug was prescribed, if it is indicated on the prescription

Other required label elements can appear elsewhere on the label in a manner not to detract from the patient centered element. This includes the name of the prescriber; date of issue, name and address of the pharmacy and prescription number or other identifying means; quantity dispensed; expiration date of the effectiveness of the dispensed drug; and the physical description of the dispensed medication including its color, shape and any identification code that appears on the tablets or capsules.

When a physician includes the medication purpose on a prescription, such as “to treat infection,” or “for blood pressure” it not only helps the pharmacist dispensing the medication, but also helps patients understand why they are taking the medication.

According to the Institute for Safe Medication Practices, improper use, overuse or underuse of medications can occur when patients don't understand the instructions on how to take their medications.

Pharmacist Stanley Weisser, Board of Pharmacy president, said studies have found that 46 percent of patients misunderstand one or more instructions on prescription labels. This is especially true for older adults.

Studies have also shown that older adults are among those most vulnerable to medication misuse because they use more prescription and over-the-counter medications than other age groups. They are likely to experience more problems with relatively small amounts of medications because of increased medication sensitivity as well as slower metabolism and elimination.

The label regulation also has a provision that requires pharmacies to have interpreters available for patients with limited English skills. If such interpreter services are not available in the pharmacy from staff, they can be secured via telephone service.

Part of the patient-centered labeling requirements also includes standardized directions for use that are to be used "when appropriate." These directions for use were developed by national researchers over the last few years. The Board of Pharmacy's website includes translations of these directions for use in Russian, Chinese, Vietnamese, Spanish and Korean.

Physicians and pharmacists working together can help with patient medication adherence.

Attachment 8

**Media Activity Report will
be provided at the meeting**