



**Improving Prescription Drug
Container Labeling in the
United States**

**A Health Literacy and Medication
Safety Initiative**

**A White Paper Commissioned by the American
College of Physicians Foundation**



The American College of Physicians (ACP) Foundation would like to express its appreciation to the United Health Foundation for a grant in support of the ACP Foundation Medication Labeling Initiative.



United Health FoundationSM



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EXECUTIVE SUMMARY

According to the Institute of Medicine (IOM) 2006 report, Preventing Medication Errors, more than half a million adverse drug events (ADEs) occur in the United States each year in outpatient settings. Problems with prescription drug (Rx) labeling were cited as the cause of a large proportion of outpatient medication errors and ADEs, as patients may unintentionally misuse a prescribed medicine due to improper understanding of instructions. Recent health literacy research has highlighted the alarmingly high prevalence of patients misunderstanding seemingly simple instructions and warnings placed on Rx container labels. The elderly, those with limited literacy skills, and individuals managing multiple medication regimens were found to be at greater risk for making errors in interpreting container label instructions.

The ability to understand Rx container label instructions is critical, both as *health literacy* and *medication safety* concerns. This is especially true since other sources of patient medication information are insufficient. Prior studies have found that physicians and pharmacists frequently miss opportunities to adequately counsel patients on newly prescribed medicines. Other supplementary sources, such as patient information leaflets and Medication Guides dispensed with the prescribed medicine are too complex and written at a reading level unsuitable for the majority of patients to comprehend. As a result, these materials are often ignored. While all of these sources are best viewed as a *system* of patient information, the Rx container label is particularly important as it is often the sole source of specific instructions received and repeatedly used by patients on how to self-administer medicines.

Despite its potential value, there are clear problems with Rx container labels. Minimal standards and regulations exist regarding their content and format, and Rx labels can vary by dispensing pharmacy. Specific dosage instructions on the container label are dependent on what the prescribing physician writes, as well as how the pharmacist interprets these instructions. While the format and content of Rx container labels may differ between and within local and national pharmacies, all share the common attribute of being unnecessarily complex and not offering a patient-friendly interface. Instead, the greatest emphasis is placed on provider-directed content.

This report reviews in detail the problem with Rx container labels in the United States. The 'best practices' in drug container labeling are summarized. Recommendations are offered to guide medical and pharmacy practice, and related state and federal policy. The overall objective of this paper is to move forward a set of evidence-based, Rx container label standards that will minimize patient confusion and promote patient awareness of how to use a prescribed medicine safely and effectively, thereby reducing risk of medication error.

Table 1. Primary Findings

Finding 1	<i>Inadequate patient understanding of prescription medication instructions and warnings is prevalent and a significant safety concern.</i>
Finding 2	<i>Lack of universal standards and regulations for medication labeling is a 'root cause' for misunderstanding and medication error.</i>
Finding 3	<i>An evidence-based set of practices should guide all label content and format.</i>
Finding 4	<i>Instructions for use on the container label are especially important for patients and should be clear and concise. Language should be standardized to improve patient understanding for safe and effective use.</i>
Finding 5	<i>Drug labeling should be viewed as part of an integrated system of patient information. Improvements are needed beyond the container label, and other sources of consumer medication information should be targeted.</i>
Finding 6	<i>Health care providers are not adequately communicating to patients, either orally or in print, about prescribed medicines. More training is needed to promote best practices for writing prescriptions and counseling patients.</i>
Finding 7	<i>Support is necessary for research on drug labeling and to identify 'best practices' for patient medication information.</i>

PROLOGUE

Since 2005, the American College of Physicians Foundation (ACPF) has sought to address the problem of limited health literacy by developing initiatives to mitigate the impact of this highly prevalent problem on health outcomes. During this time, the issue of inconsistent and confusing medication information and labeling became a primary target of the ACPF health literacy agenda. A few projects were commissioned by the ACPF, and informal activities were spearheaded to engage experts and stakeholders from academia, industry, and government. In September 2006, a meeting was held in Washington D.C. to discuss the ACPF's medication labeling initiatives and to suggest next steps for ACPF. The overall objective of the meeting was to consolidate an understanding of the broad problem of inadequate patient understanding of medication labels, and to identify a specific course of action to improve drug labeling in the United States. The meeting served as a timely response to Institute of Medicine (IOM) reports, released in July and September 2006, which targeted medication error and drug safety, respectively. Participants at this meeting included national experts in health literacy, patient safety, pharmacology, and pharmacy policy and practice. The Agency for Healthcare Research and Quality (AHRQ), the Institute of Medicine (IOM), and the Food and Drug Administration (FDA) were represented.

Participants reviewed the nature and extent of the problems surrounding medication labeling, particularly for prescription drugs. Summaries were provided from the July 2006 IOM report, Preventing Medication Errors, the FDA over-the-counter (OTC) consumer education initiatives, an ACPF-commissioned medication labeling systematic literature review, and recent health literacy research studies. Herein, this white paper presents the ACPF perspective on the current prescription medication *container* labeling system, with a focus on improving the format, content, and dosage and use instructions on the container label.

PRESCRIPTION DRUG CONTAINER LABELING: A MEDICATION SAFETY CONCERN

Patient safety remains one of the most important objectives for health care providers and organizations.¹⁻⁵ Medication errors, in particular, are the most common form of mistakes that lead to patient injury, hospitalization, and death.⁶⁻¹⁹ According to the recent IOM report, Preventing Medication Errors, approximately 1.5 million preventable adverse drug events occur each year; more than one third of these take place in outpatient settings at a cost approaching \$1 billion annually.²⁰ Both physicians and patients identify this as an area of serious concern, as a growing number of adults self-administer prescription medicines each year. Errors in ambulatory care are likely to increase as patients are self-managing a greater number of prescription and over-the-counter (OTC) medications. Two thirds of all adults use prescription drugs, representing 16 percent (\$73 billion) of all health care expenditures.²¹ According to the Medical Expenditures Panel Survey (MEPS), the average number of prescription medications filled annually by adults in the United States increased between 1996 and 2003 from 7 to 10 prescriptions. Among adults over 65 years of age, the average number of prescriptions filled increased from 19 to 27 medicines during this same time period.²¹ Further complicating the problem, elderly patients are cared for by an average of 8 different health providers, each of whom may use different instructions for the same dosing frequencies. A clear understanding of the existing failures has therefore been sought to reduce the potential for costly errors in the future.

There is a limited body of evidence detailing the possible causes of outpatient medication error. Attention to the causes of error has most often been directed to the role of the health care provider or the system in causing errors during the prescribing, ordering, dispensing or administering of a medicine.¹ This may be an appropriate focus for inpatient hospital or nursing home settings, where most studies investigating medication error have been conducted.¹⁵⁻¹⁹ However, studies estimate that many outpatient medication errors occur when patients themselves fail to administer a medicine as intended.^{6,7,13,14,22,23} For ambulatory care, the patient, rather than the provider, is ultimately responsible for correctly administering a medicine as prescribed. In this setting, the processes of quality control and monitoring of medication use shift from provider to patient.¹⁴

Given the formative role patients must play in promoting medication safety in outpatient settings, it is instructive to understand current processes that can help an individual learn how to use prescribed medicines appropriately. These include both verbal and written communication about taking medication; it is the tangible, written sources that comprise drug container labeling that are of special interest to this report. Figure 1 provides a breakdown of what specifically is meant by the broader term of 'drug labeling'. The prescription container label warrants special attention, as it often may be the only prescription drug information seen and used repeatedly by patients. As this report will detail, container labels for prescription drugs have been undervalued and neglected, despite their critical importance in conveying instructions for use to patients.

THE PATIENT PERSPECTIVE

The past 100 years have led to a fractured system of delivering adequate assurances of instructions for safe and effective use of prescription drugs to patients. In the past decade, the health literacy movement in the United States has placed greater attention on the responsibility of the health care system to support patients' ability to read, understand, and act on health information. Health literacy emphasizes the unique value of container labeling for prescription drugs as a patient source of essential health information, vital for drug safety and efficacy.

A Health Literacy Concern

Recent studies have highlighted *limited health literacy* as a potential risk factor for higher rates of outpatient medication error that are the result of improper dosing administration.^{20,22,24} Health literacy, as defined by the IOM report *A Prescription to End Confusion* and accepted by the National Library of Medicine is the "degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions."²⁴ An estimated one third to one half of adults in the United States – as many as 90 million Americans – possess limited health literacy skills, and may have trouble understanding and acting on health materials. Information in less familiar print contexts, such as prescription container labels, may be confusing and more difficult to comprehend for less literate patients.²⁵

According to the National Assessment of Adult Literacy (NAAL) of 2003, 14% of U.S. adults possess skills in the lowest level of prose and document literacy ('below basic'), and 22% are at the lowest level for quantitative literacy.²⁵ These individuals can perform only the most simple, concrete tasks associated with each of these domains. However, those with only 'basic' literacy proficiency have limited abilities and are likely to be hindered in routine daily activities. Considering individuals with basic and below basic skills combined, as many as 34% to 55% of adults in the U.S. have limited literacy skills. Estimates are significantly higher among the elderly; 60% of individuals over the age of 65 have limited levels of prose and document literacy.²⁵

Yet reading fluency and the full range of literacy skills are likely to vary with an individual's familiarity with the content of the text.^{26–28} Health materials and encounters often use difficult and unfamiliar medical terms.²⁹ Therefore, the estimates of limited health literacy using the NAAL general literacy assessment may underestimate the problem. As a response to this concern, the NAAL 2003 included a health literacy assessment designed to measure respondents' abilities to locate and understand health-related information and services. The health literacy assessment reported average health literacy scores on a scale of 100 to 500, with 500 representing the highest possible score. The assessment also reported results by grouping respondents with similar scores into performance levels based on health literacy ability. The performance levels designated by the assessment were: below basic, basic, intermediary, and proficient.³⁰ Results from the health literacy assessment showed the average health literacy scores of Americans to be lower than the average general literacy scores of adults, as measured by the NAAL. Those over 65 years of age had a health

literacy mean score of 214 (the lowest average score; threshold between below basic and basic proficiency) compared to a mean score of 256 for adults between the age of 25 and 39 (the highest average score).³⁰ The conclusion remains the same: millions of U.S. adults – especially the elderly – lack the health literacy skills that enable them to effectively use complex health materials and accomplish more challenging health-related tasks.

Sources of Patient Prescription Medication Information

The IOM Health Literacy report emphasized that the problem of limited health literacy cannot be viewed solely as a patient issue.²⁴ Rather, health literacy is a duality, reflecting both individual capability and the complexity of demands placed upon the individual by the health care system. This perspective is equally valid for medication labeling in the United States. While patients must have cognitive capacity and proficiency to read and understand labels, and apply dosage/usage instructions for proper medicine-taking behaviors, the manner in which the current health care system delivers necessary medication information to patients is inadequate.

Understanding the sources available to patients and their deficits provides for a comprehensive picture of current health system failures and remedies. The existing continuum of sources of patient medication information begins at the moment a prescription is issued to the patient by the physician (see Figure 2). Physicians, with legal responsibilities to deliver instructions on proper medication use, have repeatedly been found to be ineffective in this role.^{31–35} Research has shown physicians frequently miss opportunities to counsel their patients on how to self-administer their medicines.^{31,34} Health literacy studies have also highlighted that many physicians do not communicate health and treatment information in a manner that can be understood by patients with limited literacy skills.^{36–38} A written prescription will be passed on to patients, yet these are typically written with unfamiliar shorthand, often in Latin, and therefore of little use to patients.^{1,39,40}

If the patient leaves the physician office without the knowledge needed to correctly implement the prescribed regimen, the pharmacist, at the point of dispensing medicines, would be next in line to counsel patients. Studies have shown that pharmacists also often fail to orally communicate detailed information to patients to support their adherence with prescribed regimens.^{32,33,35} The last opportunity for counseling is the container label and accompanying print materials (container label, patient package inserts, consumer medication information, Medication Guides), which have been found to be long, complex, and written at a level too difficult for a majority of patients, regardless of literacy level, to comprehend and use.^{38,42–46}

Without accurate and available formal sources of information, individuals may seek out informal sources to learn about their medicines. Informal sources might include social networks (family, informal caregivers, friends), the internet and other reference materials. No assurances can be made to the quality, accuracy, or readability of the information provided within these sources, as their content is not regulated.^{41,42,47–49}

Health Literacy and Medication Safety

Numerous studies have found limited health literacy to be significantly associated with a poorer understanding of medication names, indications, and instructions.^{50–59} More recently, health literacy skills have been linked to requisite knowledge necessary for adherence to treatment regimens.^{22,23,60} Recently, health literacy was specifically identified within a seminal report released by the National Council for Patient Information and Education (NCPPIE).⁶¹ The report refers to health literacy as a national concern with regard to patient understanding, safe use, and proper adherence to medication regimens.⁶¹

A current and well-publicized body of research has focused on the ability of patients to read, understand, and demonstrate instructions on prescription medication container labels.^{22,23} This line of inquiry has also been supported by parallel work in human factors research, which has more broadly investigated similar measures, mostly among the elderly.^{62–68} Davis, et al conducted a multi-site study among adults receiving primary care at community health centers and found a high prevalence of patients, especially those with limited literacy, misunderstanding seemingly simple dose instructions provided on the primary label of medication containers.²² In this study, 46% of adults misunderstood at least one prescription container label they encountered. The problem extends to the auxiliary sticker labels that provide accompanying warnings and instructions for use of the medicine (see Figure 2).^{23,60} Other studies demonstrated that over half (53%) of patients, especially those with limited literacy, had difficulty interpreting text and icons commonly used on auxiliary warning instructions.²³

Beyond the container label, another recent study also found accompanying medication information materials that provide indications for use and precautions are not useful for most

patients, particularly those with limited health literacy.⁴⁶ This includes consumer Medication Guides that are required by the FDA to accompany certain prescribed medicines that have been identified as having serious public health concerns.^{69–75} Patients with limited health literacy were significantly more likely to report not having reviewed these materials. These findings are supported by earlier research studies that suggested consumer medication materials are too difficult for many patients to read.^{76–77} As a result, the patient information leaflets that accompany many prescription medications may be ignored.

Patients with limited health literacy may possess less knowledge of how to take their medicines not only as a result of difficulty with medicine labeling, but due to more limited interactions with health care providers and use of fewer alternative sources of informational support (i.e. internet, reference guides).⁷⁸ Prior research found patients with limited literacy skills to be more likely to report their physician as their sole source of health information, including for medicines taken for a chronic disease. Individuals with limited literacy are also less likely to seek out information or ask for clarification during medical encounters as a result of feelings of shame and concern over stigma for their poor reading ability.^{79–81}

A BROKEN SYSTEM

The problems associated with prescription container labeling are ultimately the result of an apparent lack of standards and regulatory oversight. This results in patients receiving medications with highly variable labels, which they frequently do not understand. This is an issue of patient safety and successful therapeutic outcomes. Current drug prescribing and dispensing practices allow for variability in container labels. A lack of integration among the existing health information systems that support an increasing number of prescribers and the majority of dispensing pharmacies also add to labeling difficulties.

The Prescriber

The container label offers perhaps the only written documentation of dosage/usage instructions for the patient, which is imparted through the physician's prescription. In most pharmacies today, whatever the physician writes is what is transcribed onto the container label. Although there may be a finite number of ways a prescription can be written, the same dose and frequency schedule for a prescribed drug may be written in several different ways (i.e. every twelve hours, twice daily, in the morning and evening, at 8am and 5pm, etc.). Physicians also use a variety of Latin abbreviations to identify drug dose and frequency, rendering the prescription uninterpretable to most patients. This becomes especially problematic as many patients, especially the elderly, may have more than one health care provider prescribing medicine. It is unclear if physicians and other prescribing health care providers receive adequate training in writing prescriptions. Although electronic prescribing offers options for enhanced safety, it is still necessary to determine what physician prescribing notations optimize patients' safe and effective use of their medications.

The Dispensing Pharmacy

The contents of labels are also highly variable depending on which pharmacy a patient selects. In a recent study, data were gathered from identically written prescriptions filled for four commonly prescribed drugs (atorvastatin, alendronate, trimethoprim-sulfamethoxazole, ibuprofen) in 6 different pharmacies (2 chains, 2 independents, and 2 grocery stores) in four diverse cities.⁸² Evaluation of the format of labels on filled prescriptions suggests that labels are not designed to optimize patient understanding of medication administration directions or warnings. The largest item on nearly all of the labels was the pharmacy logo. The average font size was also largest for the pharmacy logo, followed by medication instructions, and drug name. Auxiliary instruction and warning stickers averaged a much smaller font size (6.5 point), too small for many older patients to see without magnification.

Additionally, the label items that were emphasized were useful to identify the pharmacy and to enhance the practice of the pharmacist, but not to help patients safely and appropriately administer medication. Typographic cues (bolding, highlighting, use of color), recommended by health literacy experts to draw attention to important text, were more commonly used for the pharmacy name or logo and other items related to the pharmacy (prescription number, refill status, and quantity). Rather than emphasizing the information patients

need to take their medications safely and appropriately, current label design focuses on pharmacy brand recognition and assisting the pharmacist.

Substantial variability was also seen in the content of the labels, especially on whether or not warning/instruction stickers were used. In the reported study, between 8% and 25% of containers did not include any warning or instruction stickers. Among those that did, the variability in the content of the stickers was alarming. For the medications filled at each pharmacy, few warnings or instructions were present on more than half of the labels purchased. Among atorvastatin labels, only 42% included a warning about pregnancy, and less than 20% included directions about taking with food, taking with water, following directions precisely, and checking with a physician before starting other medications. 58% of alendronate containers included stickers instructing the patient not to lie down for 30 minutes after taking. Other warnings concerning important drug interactions and swallowing the drug whole were present on less than a third of labels. Ibuprofen containers had a broad range of warnings, but no single warning was consistently included on more than half of labels. Findings from this study suggest there is high variability in the format and content of container labels across dispensing pharmacies. More importantly, very few labels are currently designed to optimize appropriate and safe prescription medication use.

Variability also extends to how pharmacies translate physician medication instructions. In a follow-up study, researchers investigated how dosage instructions, written with common Latin abbreviations, were interpreted by various pharmacies.⁴⁰ Considerable differences were noted (see Table 2). Among the 85 labels evaluated, dose frequency was omitted on 6% of instructions (“Take 1 tablet for cholesterol”).⁴⁰ Administration timing was explicitly stated on only 2% of instructions (“in the morning”). All four prescriptions noted earlier were written with an indication, yet pharmacies transcribed this onto 38% of labels. The prescription for alendronate stated to not lie down for at least 30 minutes after taking; this was transcribed with 50% of instructions. A total of 27% of the translated instructions had a Lexile reading grade level above a high school level.²³

Table 2. Physician-Written Prescriptions and Pharmacy Interpretations.

Prescription	Examples of Pharmacy ‘Sig’ Interpretations
Lipitor 10 mg tabs Take one tab QD Dispense #30 Indication: for high cholesterol No refills	- “Take one tablet daily.” - “Take 1 tablet by mouth for high cholesterol.” - “Take one (1) tablet(s) by mouth once a day.” - “Take one tablet by mouth every day for high cholesterol.”

Prescription	Examples of Pharmacy 'Sig' Interpretations
Fosamax 5 mg tabs Take one tab QD Dispense #30 Indication: osteoporosis prevention Do not lie down for at least 30 minutes	<ul style="list-style-type: none"> - "Take 1 tablet by mouth daily." - "Take one tablet by mouth every day for osteoporosis prevention. Do not lie down for at least 30 minutes after taking." - "Take 1 tablet every day, 30 minutes before breakfast with a glass of water. Do not lie down." - "Take one tablet every day."
Bactrim DS tabs Take one tab BID Dispense #6 Indication: UTI No refills	<ul style="list-style-type: none"> - "Take one tablet by mouth twice daily for UTI" - "Take one tablet by mouth twice daily for urinary tract infection." - "Take 1 tablet by mouth 2 times a day." - "Take 1 tablet twice daily for 3 days."
Ibuprofen 200 mg tabs Take 1–2 tabs TID PRN pain Dispense #30 No refills	<ul style="list-style-type: none"> - "Take 1 to 2 tablets by mouth as needed for pain." - "Take 1 to 2 tablets by mouth three times daily as needed for pain." - "Take 1 to 2 tablets by mouth as needed for pain ** Not to exceed 4 times a day" - "Take 1 to 2 tablets 3 times a day as needed for pain."

Health Information Technology

Tremendous advances have been made in the use of health information systems that support the prescribing and dispensing of medication. The 2006 IOM report, *The Future of Drug Safety*, directs attention to e-prescribing and the importance of health technologies for surveillance of errors and events but also to rapidly communicate risk information.⁸³ As more medical practices are incorporating electronic health records, many of these systems are now setting standard 'sig' messages for prescribing medications for efficiency and patient safety purposes.⁸⁴ At the point of dispensing, pharmacy systems also have been using information systems to support drug labeling. This includes default standards for translating prescriber instructions and including auxiliary warnings, with set parameters for label content and format.^{85,86} Currently, the Agency for Healthcare Research and Quality (AHRQ), Center for Medicare and Medicaid Studies (CMS), and National Coalition for Prescription Drug Programs have been working to develop a finite list of standard, codified 'sig' lines to improve care and efficiency specifically for electronic prescribing practices.⁸⁷ A major problem that has been recognized by these organizations is the discordance between the uniform practices being developed through electronic health records at the point of prescribing and those systems in place within a majority of pharmacies in the U.S.. Linking the technology on both sides to ease



communication and avoiding a need for interpretation at dispensing will be an essential goal for achieving a truly standard, integrated system of patient medication information.

A BRIEF HISTORY OF DRUG LABELING

The looming problem of prescription drug container labeling is best appreciated after having a basic understanding of the relevant historical events leading up to the present circumstances. Since the formal establishment of the modern Food and Drug Administration (FDA) as a regulatory agency in 1906, four recurring themes related to drug labeling are apparent. First, oversight of drug labeling has always been a focus of the FDA, and the agency's role has gradually evolved with expanding regulatory power. Second, labeling for prescription-only medicines, in particular, is based on the assumption that physicians and other prescribers adequately communicate medication instructions to patients. Third, FDA-issued requirements for prescription drug container labeling practices are exceptionally vague. Finally, container labels for prescription-only medicines are primarily governed at the state level, and most states offer minimal guidance.

Early Attention to Drug Labeling

Instructional labels attached to vials containing the various medicines available have been in existence for centuries. Prior to the turn of the 20th century, drug container labels were designed for physician-pharmacist communication; they contained minimal content typically written in Latin abbreviations.⁸⁸ The United States Pharmacopeia (USP) was formed in 1820 to create a system of standards that would ensure quality control and drug safety. At that time, only 217 drugs met the criteria for inclusion as "most fully established and fully understood".⁸⁹ With the few possible exceptions of certain state regulations, there were no laws in place governing what could or could not be stated on the container label.⁸⁸ The Pure Food and Drugs Act of 1906 was the beginning of many federal legislative responses to promote accurate and safe practices in the labeling and marketing of drugs.

The federal government response was warranted by an increasing incidence of consumer reports and investigations of patent or 'quack' medicines. Many widely-used products were ineffective, addictive, or even lethal.⁸⁸ This new law focused on the regulation of product labeling rather than pre-market approval. The passage of the Pure Food and Drugs Act marked the beginning of the modern era of the FDA, and with this legislation came the beginning of a limited set of federal labeling standards. Specifically, drugs defined with standards of strength, quality and purity in the USP could not be sold in any other condition unless the variations from the standards were plainly stated on the label.⁸⁸ The new law required the contents and quantity of food and drug products be clearly identified on the label attached to the container or package. Drug labels could not be false or misleading, and the presence and amount of eleven dangerous ingredients, including alcohol, heroin, and cocaine, had to be listed on the label.⁸⁸

What follows throughout the early decades of the 20th century is a pattern of extending federal regulatory oversight for drugs, with two distinct classifications now emerging: over-the-counter and prescription-only. This was primarily driven by a growing number of cases of unintentional drug addiction and harm. The Harrison Narcotics Act of 1914 required pharmacies to be licensed (at a cost) to dispense narcotics, and for these drugs to require a physician prescription.⁹⁰ Prior to this time, pharmacists usually followed physician recommendations and

any pertinent state laws concerning dispensing practices. Problems began to emerge when physicians complained about the ability of pharmacists to dispense refills to patients for prescribed medicines without the authorization of the physician. The Harrison Act initiated the early distinction in federal statutes between the modern classifications of prescription and over-the-counter medicines, but only for a distinct class of drugs.

With growing concern over a new class of sulfa drugs among other new therapeutic agents, the Food, Drug, and Cosmetics Act of 1938 (FDCA) further grounded the FDA as an agent of public health, deeming many more new drugs too much of a hazard for self-medication and requiring a physician's prescription for use.⁹⁰ New labeling requirements were issued with the FDCA, requiring drug labels to explicitly state to consumers all ingredients, adequate directions for use, and to include warnings of potential dangers if not administered appropriately. With the new law, manufacturers had to submit a "New Drug Application" (NDA) before the drug would be approved by the FDA. The NDA had to include information about the drug and its safety, along with prescribing information. If a medicine had a narrow therapeutic margin with apparent risks, making it difficult to detail adequate instructions for safe use, the FDA's regulations required the drug label to include a statement restricting access by mandating that the drug be dispensed only through a physician's prescription. Specifically the following statement was to be included on the label: "To be used only by or on the prescription of a physician".⁹⁰ This is referred to as the prescription legend, which is still required on prescription medicine container labels to this day (although this statement was shortened to 'Rx Only' in 2000).

Within two months of the passage of the FDCA, the FDA began to identify drugs such as the sulfas that could not be labeled for safe use directly by the patient—they would require a prescription from a physician. Labeling manufacturers were increasingly recognized as a serious problem. Drugs that were viewed as safe for over-the-counter use were marketed as prescription-only to avoid liability in the container/package labeling requirements for detailed instructions for use and safety warnings.⁹⁰ Laws remained unclear for prescription labeling, specifically, as the FDA assumed that physicians and pharmacists were orally communicating necessary usage directions and warnings to patients for prescribed medicines. Hence, less attention was given to the labeling on prescription drug containers or any accompanying marketing literature provided by the manufacturer. In addition, variable refill restrictions made it still possible for an individual to continue a prescription medicine, and manufacturers advertised directly to consumers to recommend their product to friends.⁹⁰ To confuse matters more, different manufacturers of the same drug often would take contradictory approaches to marketing their medicine to patients. One label might state the drug was for prescription use only, while another would be promoted for over-the-counter sale.

The Durham-Humphrey Amendment of 1951 helped put an end to some of the consumer confusion left in the wake of the FDCA, by compiling a list of medicines of the day that should be dispensed only with a physician's prescription.⁹⁰ The Amendment also established a broad outline for what constituted a prescription drug, as those medicines that were 1) habit forming, 2) toxic thereby requiring physician supervision, or 3) new drugs approved by the FDA with safety precautions.⁹⁰ Refills were addressed and these required

physician authorization in the Durham-Humphrey Amendment, along the regulatory assumption of the FDA. Over-the-counter medicines were required to have adequate label instructions and warnings to instill safe use by the consumer, without physician consultation. However, this was not necessary for prescription-only drugs, as again it was expected access required physician consultation and information would be delivered verbally at that time. Interestingly, the Durham-Humphrey Amendment still left the ultimate determination of whether a drug would be prescription or over-the-counter to the drug manufacturer's discretion.⁹⁰

Beyond the Bottle: The Learned Intermediary

In 1966, a pharmaceutical liability suit, *Sterling Drug Inc. v. Cornish*, established the physician as the "learned intermediary" with responsibility to communicate drug warnings passed on by the manufacturer to patients.⁹¹ According to the learned intermediary doctrine, a prescription drug manufacturer fulfills its legal duty to warn a patient by adequately warning the prescribing physician. Of note, the duty to warn only the physician (and not the patient) is an exception to the general rule of law that adequate warning must reach the ultimate consumer in order for the manufacturer to avoid product liability in the case of harm. As the number of drugs labeled prescription only increased, manufacturers continued to maintain autonomy over labeling practices for these drugs. With the physician as learned intermediary, it was not viewed as necessary for prescription medicine labels to meet what constituted adequate written instructions and warnings for patients, as required under the FDCA.

With an increasingly litigious climate and society demanding more public disclosure, the need for consumer-directed prescription drug information was recognized. The Fair Packaging and Labeling Act of 1966 continued the FDA legacy of demanding honest and informative product labeling from the manufacturers themselves.⁹² In line with a much earlier 1948 Supreme Court ruling in *Kordel v. United States* that stated supplementary materials not physically attached to the drug container could still be viewed as part of the product label, the Fair Packaging and Labeling Act mandated the inclusion of patient-directed package inserts written in lay language for all prescription drugs. This was to give patients more detailed instructions and warnings about a prescribed drug's risks and benefits, in light of container label space limitations. By the end of 1968, the first 'patient package insert', or accompanying drug information sheet was issued for the asthma inhalant isoproterenol.⁹³ Not until 1970 with the issuance of a package insert for oral contraceptives did this requirement draw public attention.⁹⁸

In 1979, the FDA attempted to require drug manufacturers to create patient package inserts for all prescription drugs. The FDA quickly revoked this regulation in 1981 after receiving criticism for the program by industry and health care provider organizations. In its place, drug manufacturers made a good faith agreement to 'self-regulate' the industry, and generate "consumer medication information" (CMI) to be distributed with prescription medicines. In 1995, the Medication Guides program was unveiled at the FDA, which required the industry to generate yet another patient information form, for certain

prescription drugs deemed to be of “serious public health concern”.⁸⁸ Medication Guides are similar to the earlier patient package inserts, and are now the only consumer-directed materials for prescription drugs with explicit standards in place for their development, and to which the FDA still maintains regulatory oversight. Since 1995, more than 50 prescription medications and/or drug classes have been required to include Medication Guides. With the onset of this program, the definition of drug labeling had now expanded to include the container label, package insert, consumer medication information, and Medication Guide. The prescribing information, or ‘prescriber’s insert’, that has been required by law since 1938 for prescription-only medicines, is technically part of the label but is directed to the physician rather than the patient.

In 1997, The Keystone Dialogue, initiated by the Department of Health and Human Services and including the FDA, pharmacist associations, and the National Association of Boards of Pharmacy, was charged with developing an action plan for improving drug labeling. Recommendations targeted improvements in the reading ease of consumer medication information in order for these print materials to be accessible and useful. The published report called for consumer medication information to be written at a sixth to eighth grade level and for improved format and organization.⁷⁵ These were recommendations only, as a review of FDA-approved materials a decade later found little improvement in the quality of patient information.

The most recent labeling effort by the FDA to ensure patient understanding of appropriate prescription drug use was the June 30, 2006 revision of 21 CFR 201.56 and 201.57, “Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products”. While the new law had the patient in mind, its provisions reflect the powerful role of the learned intermediary in providing essential information to the ultimate medication consumer. Revisions specifically targeted modifications to the prescriber’s insert label directed to physicians. According to the new law, all inserts must contain a *Highlights* section summarizing drug benefits and risks, as well as a table of contents. Another new section, *Patient Counseling Information*, is also now included in inserts to help summarize for physicians what information about a particular drug should be conveyed to patients. This was the first change to the package insert in 25 years. However, the package insert is aimed at educating physicians rather than patients, and these changes will likely offer little relief to patients when they pick up their prescriptions at the pharmacy.⁹⁴

The Modern Drug Container Label: Contents and Oversight

Under 21 CFR 201 of the FDCA, the FDA now requires the following information be present on the prescription drug container label: drug name, pharmacy name and address, serial/lot number of the prescription, prescribing physician name, patient name, and instructions for use. State boards of pharmacy may impart their own additional standards for container label content and format. To date, only minimal regulations have been added by states, although enough to require national pharmacy chains to generate 31 different label styles across the 50 states.

Without explicit FDA regulatory guidance, it still remains unclear what constitutes 'adequate' label instructions and warnings according to the FDCA for the more than 13,000 FDA-approved prescription medicines in use today. With the recent dominance of direct-to-consumer advertising and the 1999 ruling in *Perez v. Wyeth Laboratories, Inc.*, the pharmaceutical industry has had to assume greater liability to directly warn consumers, beyond the learned intermediary, of any potential risks associated with using a particular medicine.⁹¹ Such risks have usually been conveyed through the prescriber's insert (for providers) and CMI (for patients), and not directly on the container label, due to space issues.

With limited space on the primary container label which detail dosage/use instructions, auxiliary 'warning' stickers had been included with bottles as early as the late 1950s. These secondary container labels provided special instructions and precautions, often given orally to patients by the pharmacist, to support safe patient administration. However, no regulations have existed regarding the use of these auxiliary stickers either. Despite the potential value of these stickers, the accuracy of the specific instructional and/or precautionary messages has not been confirmed through any systematic process derived in pharmacological evidence.

SETTING STANDARDS: AN EVIDENCE-BASED DRUG CONTAINER LABEL

While limited, there is evidence available to detail 'best practices' for improving dosage/usage instructions written by the prescribing physician, and the format and content of prescription medication container labels designed by the dispensing pharmacy.⁹⁵ Perhaps most importantly, the use of standard and more explicit dosage/usage instructions can improve patients' functional understanding of how and when to take a medicine (i.e. take two tablets by mouth twice daily vs. take 4 tablets a day vs. take 2 tablets in the morning, and take 2 tablets in the evening).²² Shrank and colleagues summarized known evidence for best practices in labeling format and content, such as: increasing font size, using clear and simple language, using headers, and placing a more appropriate emphasis on organizing label content around what is most important for patients (i.e. drug name, dose, dosage/usage instructions, patient name, doctor name, quantity, refill information) instead of the provider content (i.e. pharmacy name/logo, phone number, national drug code number).⁹⁵

The field of health literacy also offers appropriate recommendations on how best to present print medication information to lower literate audiences. For instance, sans serif font should be used, avoidance of all capital letters for words and phrases, and using numbers instead of the text equivalent (i.e. 2 instead of "two").^{22,95} When possible, text should be as large as 12 point font to display patient dosage/usage instructions. Icons for drug warnings have previously been found to be confusing for many older patients and those with limited literacy skills, and should be minimized in practice. A complete list of evidence-based, recommended standards for format, content, and instruction is detailed in Table 3.

Table 3. Description of Standards for an Enhanced Rx Container Label.

Proposed Standard	Description
1. <i>Use explicit text to describe dosage/interval in instructions.</i>	Dosage/usage instructions must clearly separate dose from interval, and provide the explicit frequency of the drug (i.e. "take 4 tablets each day. Take 2 tablets in the morning, and 2 tablets in the evening" vs. "take two tablets by mouth twice daily"). These explicit dose/use instructions will be standardized by the pharmacy to avoid physician variability for the same dose frequency.
2. <i>Use a recognizable visual aid to convey dosage/use instructions.</i>	A visual aid 'matrix' can help patients identify and support the explicit text dosage/usage instructions, following a familiar format to cue patients (pill sorter box; morning (7am-9am); noon (11am-1pm); evening (4pm-6pm); night (8pm-10pm)). A tablet icon will be used to identify the appropriate dose.

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Proposed Standard	Description
3. <i>Organize label in a patient-centered manner.</i>	Patient-directed information must be organized in a way that best reflects how most patients seek out and understand medicine instructions. Patient-directed content will be at the top of the label, while provider-directed content will be placed at the bottom of the label. Drug name and specific dosage/usage instructions will be placed in greatest prominence.
4. <i>Include distinguishable front and back sides to the label.</i>	The Rx container label should have two distinct sides – a front (primary) and back (auxiliary) side on the bottle. The primary label will contain patient information (drug name, dose, dosage/usage instructions, patient name, doctor name, quantity, refill information) and provider content (pharmacy name/logo, phone number, national drug code #). The back should contain all appropriate warning and instruction messages and icons, supplanting the use of stickers.
5. <i>When possible, include indication for use.</i>	While Rx approval status and confidentiality may limit inclusion of indications for use, prior studies suggest this is very helpful to patients.
6. <i>Simplify language, avoiding unfamiliar words/medical jargon.</i>	Language on the label, will avoid the use of unclarified medical jargon, and common terms and sentences will be used only. While readability formulas and software are not recommended for short excerpts of text such as what is included on Rx labels, the principles established by the Suitability Assessment of Materials by Doak, Doak, and Root for maintaining simple language can guide the simplification process. Feedback should also be sought from consumers.
7. <i>Improve typography, use larger, sans serif font.</i>	A standard for minimum font size (12 pt) will be set for patient name, drug name, and specific dosage-usage instructions (both in text and in matrix). Health literacy and adult education researchers recommend the use of Sans-Serif font (i.e. Arial) to more clearly present print text information to new adult learners. Patient information on front and back labels will be 12 pt font. Use of all capital letters should be avoided; the first letter of words in text will be capitalized only.

Proposed Standard	Description
8. <i>When applicable, use numeric vs. alphabet characters.</i>	Our recent research efforts (see Section C), and a prior study, provide evidence that presenting numbers instead of the text equivalent (i.e. 2 vs. two) was more helpful to patients for understanding and more rapidly processing dosage/usage instructions.
9. <i>Use typographic cues (bolding and highlighting) for patient content only.</i>	Bolding and highlighting will be used for patient-centered information only. Drug name and dose will be highlighted, dosage/usage instructions bolded.
10. <i>Use horizontal text only.</i>	Several national pharmacy chains place text for warning and instruction messages vertical to the Rx label; requiring the patient to turn the bottle to read. This may create further difficulty among older adults. Only include horizontal text on the label.
11. <i>Use a standard icon system for signaling and organizing auxiliary warnings and instructions.</i>	Work towards a standard set of icons, or consider a single icon to flag patients that a warning exists for the prescribed medicine. Warnings will use 12 point font.

Current FDA Over-The-Counter (OTC) product labeling standards may provide additional guidance to future strategies to be taken with prescription medications. OTC products, such as “Drug Facts”, have already been developed with health literacy considerations in mind, utilize a standard format, and have been marketed to the public, increasing their familiarity and usability. While not all OTC labeling standards are applicable for prescription medicines, patients would likely benefit from a more familiar and consistent format, especially if this could extend to dosage/usage instructions.

SPECIFIC REPORT FINDINGS

Ideally, medication labeling should be viewed as a system of information, with key components communicated to the prescriber, the dispenser, and ultimately to patients. The work of this group has used the lens of health literacy to target patients' critical need for clear and concise prescription medication instructions to support safe and effective use. Based on the evidence and potential impact for reducing confusion that may lead to medication error, standardization of the container label's content and format, including dosage instructions, is proposed as a primary evidence-based finding that the committee viewed as necessary for resolving the current prescription labeling problem. It is anticipated that several measures will be required to address the development of low literacy-appropriate patient information leaflets and Medication Guides, and provider education and training programs to increase medication counseling and best practices for writing prescriptions.

The findings of this report support the exploration into a standard label format that may potentially include set key intervals (i.e. morning, noon, evening, bedtime) that can most precisely identify dose frequency. Currently, preliminary research activities are under way by members of the committee to investigate the efficacy of a matrix visual aid on the container label to improve patient comprehension of dosage instructions. However, before this or any other standards can be recommended, perspectives from pharmacology, pharmacy and from prescribing clinicians should be sought. More research is needed to support future actions to be taken with regard to prescription medication labeling, and all modifications to the existing labeling format should be properly evaluated.

The Committee concluded with the following findings:

- 1. Inadequate patient understanding of prescription medication instructions and warnings is prevalent and a significant safety concern.** Health literacy research has highlighted the high prevalence of patient misunderstanding of dosage instructions and auxiliary warnings placed on Rx container labels. The elderly, those with limited literacy, and individuals managing multiple medication regimens are at greater risk for misinterpreting prescription instructions.
- 2. Lack of universal standards and regulations for medication labeling is a 'root cause' for medication error.** More than a third of all reported adverse drug events occur in ambulatory care settings, where patients primarily assume quality control over prescription medication administration. Patient misuse is a common occurrence, and the clarity and complexity of medication dose/use instructions varies greatly by dispensing pharmacy. State and federal agencies involved in consumer medication information and labeling are not united in efforts to provide regulatory guidance.
- 3. An evidence-based set of practices should guide all label content and format.** A major problem for prescription drug labeling relates to content inclusion. Efforts need to be directed at minimizing information placed on the label container, particularly auxiliary instructions supporting the safe use of the product. Only warnings and instructions that are supported by pharmacological evidence, or that are otherwise thought to significantly aid the patient in

self-administration should be placed on the label. If a warning or instruction message is to be recommended for a specified drug to be on the container label, then it should be required. This would limit the existing variability between and within pharmacies.

4. Instructions for use on the container label are especially important for patients and should be written in the most clear, concise manner. Language should be standardized to improve patient understanding for safe and effective use. Variability and confusion regarding prescription drug label dosage/usage instructions is especially problematic. While auxiliary warning and instructions may vary by pharmacy, the actual instructions for dosage and use for a medicine will often vary by prescribing physician. Explicit instructions that segregate dose (number of pills to be taken at one time) from frequency (number of times per day) are more helpful to patients. Standardized, evidenced base dosage/usage instructions with limited variability would provide patients with more useful information, and offer improved drug safety for patients.

5. Drug labeling should be viewed as an integrated system of patient information. Improvements are needed beyond the container label, and other sources of consumer medication information should be targeted. Consumer-directed materials that accompany the pill bottle container currently do not meet acceptable standards set for the design of health information for patients with limited literacy skills. Medication Guides, patient information leaflets, and other supplementary sources of medication information should follow the same patient-oriented schema for presenting content as the container label, and be simplified following current health literacy principles. Patients need to be involved in the re-design of these materials, and considerations of re-design should focus on all the components of the label as a system of information.

6. Health care providers are not adequately communicating to patients, either orally or in print, for prescribed medicines. More training is needed to promote best practices for writing prescriptions and counseling patients. Physicians, nurses, physician assistants and pharmacists have previously been reported as missing opportunities to adequately counsel patients on how to administer prescribed regimens. While recent FDA actions mandate content in the package insert to aid providers on what to convey to patients about specified medicines, additional training and quality improvement efforts are needed to ensure the occurrence of these practices.

7. Research support is necessary to advance the science of drug labeling and identify 'best practices' for patient medication information. Ultimately, funds should be allocated to support research that can systematically review the scientific evidence and detail the necessary content for inclusion on prescription container warning labels and supplementary patient medication information materials. Likewise, health services and human factors research is needed to test new labeling strategies that incorporate known 'best practices' and determine whether the changes can improve patient understanding, behaviors, and even health outcomes.

CONCLUSION

The ACPF Medication Labeling Technical Advisory Board has proposed several changes for prescription drug labeling, perhaps most notable being that dosage/usage instructions on the container label be a critical and primary focus for establishing clear standards. The importance of the container label should be reiterated as the most tangible and repeatedly used source of prescription drug instructions for use. In fact, it may be the 'last line' of informational support on how and when to take a prescribed medicine. The Advisory Board agreed that prescription medication labeling should be viewed as a *system of information*, and additional efforts must also seek to standardize and improve labeling beyond the primary prescription container label.

It is anticipated that this report will engage policymakers, researchers, and clinicians to work toward an integrated and standard system of patient medication information. The IOM report *Preventing Medication Error* issued a call to action to improve patient-directed medication information, including labeling and provider-patient communication. To go one step beyond the report, an agenda should be detailed that targets the prescription drug container label, and then works to integrate other formal information sources. Lessons from both the field of health literacy and human factors design should be observed. Above all, this work must be done with patients as partners in the process, to ensure the best deliverables possible.

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