CHAPTER 5

Pharmaceutical Labeling in the US

Cathleen O'Connell, PhD, MS, RPh, Susan Merchant, Zahra Martinez, PharmD, RPh, and Jocelyn Jennings, MS, RAC-US, RAC-Drugs, RAC-Devices, FRAPS

Introduction

A product's labeling presents the information necessary for a product's safe and effective use. It is the culmination of drug development and the essential element for drug approval. Labeling approval by the US Food and Drug Administration (FDA) signals the point at which a new drug or biologic may be sold throughout the US and its territories. Beyond its role as the information component of a product, pharmaceutical labeling in the US has implications for the product's commercial success as well as global influence and the potential for liability actions. Labeling, therefore, attracts intense scrutiny at the highest levels of company management across many different functions, as well as from interested parties outside the company.

Prevailing Laws and Authorities

Congress established authority for the regulation of drugs through the Federal Food, Drug, and Cosmetic Act (FD&C Act) from which the FDA derives its oversight authority. Other laws underlying the regulation of pharmaceutical labeling are described in **Table 5-1**.[1-10]

In addition to the FDA, other agencies that influence requirements for pharmaceutical labeling include the following:

- Drug Enforcement Agency (DEA): oversight of controlled substances[3]
- US Customs and Border Protection Agency: country of origin labeling requirements for substances manufactured ("substantially transformed") outside the US (19 CFR 134.11)[11,12]
- US Pharmacopoeia (USP): labeling standards for the expression of purity and potency, nomenclature, and package warnings statements for certain products[13]

Prescription Medicines

As defined in the FD&C Act, the label of a pharmaceutical product is the "display of written, printed, or graphic matter upon the immediate container of any article."[1] Any information required on the label also must appear on the outer wrapper or container or be visible through the container, if any. The FD&C Act defines the broader term, *labeling*, as "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2)

Table 5-1. Laws and Amendments Relating to Pharmaceutical Labeling in the US

Laws and Amendments	Labeling Implications
Federal Food, Drug, and Cosmetic Act (FD&C Act, 1938)	Set standards for safety and efficacy for marketed drug products; defined *label* and *labeling*; established qualifications that labeling must: • Not be false or misleading [§502(a)] • Include adequate directions for use [§502(f)] • Be supported by substantial evidence [§505(d)][1]
Durham-Humphrey Amendment to FD&C Act (1951)	Distinguished prescription from nonprescription products, with labeling differentiated by the information needs of healthcare professionals and consumers.[2]
Kefauver-Harris Amendment to FD&C Act (1962)	Set standards for safety and efficacy for marketed drug products, through evidence reflected in labeling.
Controlled Substances Act (1970)	Places all substances regulated under existing federal law into a labeled "schedule" based on medical use, potential for abuse, and safety or dependence liability.[3]
Fair Packaging and Labeling Act (1966)	Requires labeling of consumer products, including pharmaceuticals, to disclose identity, net contents, and name and address of the manufacturer, packer, or distributor. It further authorized regulations to prevent consumer deception.[4]
Federal Anti-Tampering Act (1983)	Prohibits tampering with consumer products that affects the labeling or renders it materially false or misleading with intent to cause harm.[5]
Food and Drug Administration Modernization Act (FDAMA, 1997)	Section 126 eliminated legend for prescription medicines ("Caution: Federal Law Prohibits Dispensing without a Prescription"); introduced "Rx only."[6,7]
Best Pharmaceuticals for Children Act (BPCA, 2002)	Incentivized pediatric research and expanded labeling on the use of pharmaceutical products in children.[8]
Food and Drug Administration Safety and Innovation Act (FDASIA, 2012)	Section 904 addressed best practices for accessibility of prescription container labels by the visually impaired and blind; Section 1140 required the Comptroller General to conduct a study on the use of electronic prescription drug labeling.[9]
Food and Drug Administration Amendments Act (FDAAA, 2007)	Section 901(a) added a new Section 505(o)(4) to the FD&C Act, giving FDA authority to require sponsors to amend approved labeling in response to new safety information.[10]

accompanying such article."[1] This term's scope has been extended through legal interpretation of the condition "accompanying such article" to include information not physically packaged with the product.[14] The familiarly termed *package insert* includes the product's prescribing information as well as any FDA-approved patient labeling. (See chapter on Patient Labeling in the US.) The PI is packaged with the product and also is disseminated electronically via the company's website(s) and through the National Library of Medicine's DailyMed website.[15]

As articulated by the FDA:

> "A prescription drug product's FDA-approved labeling (also known as 'professional labeling,' 'package insert,' 'direction circular,' or 'package circular') is a compilation of information about the product, approved by FDA, based on the agency's thorough analysis of the new drug application (NDA) or biologics license application (BLA) submitted by the applicant. This labeling contains information necessary for safe and effective use. It is written for the healthcare practitioner audience, because prescription drugs require 'professional supervision of a practitioner licensed by law to administer such drug'" – Section 503(b) of the act (21 U.S.C. 353(b)).[16]

Prescribing information must be an informative and accurate summary of essential information to support healthcare professionals in the product's

safe and effective use.[17] To preserve the condition of not being false or misleading, as stipulated in the FD&C Act, labeling must be updated whenever new information becomes available.[18] It is important to appreciate that a product's prescribing information does not set the standard of care for its indications and is only one resource available to guide prescribers in their medical practice. Further, once a prescription medicine is approved for one or more indications, prescribers sometimes use it for other, unapproved indications not included in the labeling, also referred to as off-label use.[19]

The target readership of prescribing information is healthcare professionals. However, it also is closely read by others for a variety of reasons.

- Health authorities – In addition to the FDA, labeling approved in the US serves as a reference for regulatory submissions elsewhere in the world and may influence the content of prescribing information in other regions.
- Pharmacovigilance professionals – Current prescribing information is used as a reference in safety reporting to determine if an adverse event is "labeled" or "unlabeled."[20]
- Marketing – As the basis of promotional activities, it will be used in the development of marketing strategy.
- Competitors – Approved labeling will be scrutinized for commercial purposes and may be used as a starting point in the development of labeling for new products.
- Liability attorneys – Labeling attracts the close attention of liability attorneys both within and outside the company.

While medical professionals' needs should be the primary focus when drafting prescribing information, consideration of other audiences for this document may influence decisions about content and specific wording.

Preparing for Submission

Labeling content is developed by a cross-functional team of professionals responsible for various aspects of the product's research, development, marketing, and regulatory compliance. Specifically, drafting the prescribing information requires input from individuals who can speak to underlying data from all research and development stages. Marketing professionals will identify key commercial messages based on brand strategy. A team may need to involve a liability attorney to ensure careful wording of certain text, such as a particular warning, or provide other legal guidance related to informing healthcare professionals about the product. Medical affairs professionals may be recruited in later labeling development stages to suggest edits to wording or expand content details to prevent confusion for healthcare professionals unfamiliar with the drug that otherwise would prompt questions to the company. Finally, those directly responsible for drafting the labeling manuscripts may be individuals responsible for regulatory activities supporting the product's registration in the US, such as US regulatory professionals, or they may be dedicated labeling specialists, if a company has such a department.

The team needs to carefully plan labeling text development based on the expected availability of mature drafts of source documents. Overviews and summaries are used most often as source documents to support labeling statements, as they synthesize information from individual study reports written well before labeling text is being finalized. Discrete study reports are used when integrated documents do not support a particular claim or statement in the prescribing information. (All content must be scrupulously annotated to sources that support the labeling text. It is critical that the team collaborate closely to ensure precise annotation to supporting documents to substantiate every statement in the prescribing information.)

The formal review process for prescribing information (and any patient labeling the sponsor submits to the FDA) often involves senior management from each functional area. Team members should communicate their labeling strategies to their functional management and inform them about the status of supporting data to ensure final labeling documents are aligned with development objectives.

Reviews may be scheduled after labeling sections are completed (e.g., nonclinical, clinical

pharmacology, chemistry, manufacturing, and controls [CMC]) or in one or more marathon review sessions of the entire draft. It cannot be overemphasized that any delay in finalizing source documents is likely to impact completion of labeling work. Reviewer comments on labeling documents, such as table format, may influence final source document versions. As prescribing information and any patient labeling are the last dossier items to be completed, such a delay may ultimately affect submission timing.

Quality checks of labeling documents, including format verification, should be conducted prior to senior management review to ensure the FDA's template requirements are met and all statements mandated by regulation are included. Given the ultimate, practical purpose of the prescribing information, text readability also should be assessed. Following internal approval by senior management, a final content quality review should be conducted and all annotations verified to ensure the appropriate source document sections are referenced to support each label statement.

Prescribing Information

General Requirements

Prescription medicine labeling requirements reflect attention to healthcare professionals' needs for product information, including adequate directions for use. The FDA has implemented and continues to update regulations and guidances for labeling development and maintenance, so a search of the agency website is recommended to verify current prevailing requirements before beginning work on labeling. Current and comprehensive information is available on the FDA's website, including guidance documents and presentations on prescribing information, patient labeling, carton and container labeling, and more.[21]

Regulations (21 CFR 201.56) specify that prescription drug labeling must:

- "…contain a summary of the essential scientific information needed for the safe and effective use of the drug.
- "…be informative and accurate and neither promotional in tone nor false or misleading in any particular…the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.
- "…be based whenever possible on data derived from human experience. No implied claims or suggestions of drug use may be made if there is inadequate evidence of safety or a lack of substantial evidence of effectiveness."[17]

Specific Requirements

Non-promotional labeling components required for FDA submission as the basis of a new drug or biologic product's marketing approval include:

- Prescribing information, submitted as Structured Product Labeling;
- Any required patient labeling; and
- Trade and sample packaging, including the immediate container label.

Requirements for each of these components are detailed in 21 CFR.[22]

The Immediate Container Label

Table 5-2[1,13,23-30] specifies the required elements for the label on the immediate container of prescription drug and biological products.

Content and Format of the Prescribing Information

In January 2006, the FDA introduced the Physician's Labeling Rule, or PLR, which substantially changed requirements for prescription drug labeling content and format in the US. These changes included the introduction of new features, such as a Highlights section and table of contents, and the reordering of information to ensure the most important information for prescribers appears at the beginning. As described in the PLR Final Rule, these revisions were intended to "…make it easier for healthcare professionals to access, read, and use information in prescription drug labeling. The revisions will

Table 5-2. Required Elements for Container Labels of Prescription Drugs and Biologics[a,1,13,23-30]

Labeled Element	Regulation(s)
Name and address of manufacturer, packer, distributor	21 CFR 201.1;[23] 610.0, 610.64[24]
National Drug Code (requested, not required)	21 CFR 201.2[23]
Statement of ingredients, quantity and proportion	21 CFR 201.10, 100[23]
Lot number	21 CFR 201.18; 610.60[23,24]
Expiration date	21 CFR 201.17, 211.137;[23] 610.60;[24] ICH Q1A(R2) Section 2.2.10[25,26]
Storage conditions	21 CFR 205.50;[27] 610.60;[28] USP-NF,[13] ICH Q10A(R2) Section 2.2.10[25]
Bar code	21 CFR 201.25[23]
Statement of identity (established name)	21 CFR 201.10, 50;[23] 610.60[24]
Declaration of net quantity of contents, strength	21 CFR 201.51[23]
Recommended dosage	21 CFR 201.55, 100;[23] 610.60[24]
Route of administration (if not oral)	21 CFR 201.100[23]
Country of origin (if different from the US)	19 CFR 134.11[29]
"Rx only"	21 CFR 201.100;[30] 610.60[28]
Directions specifying type of container to be used in dispensing	21 CFR 201.100[23]
Product identifier	Food, Drug, and Cosmetic Act Subchapter 8 – Pharmaceutical Distribution Supply Chain (§581 and §582)[1]

[a] See 21 CFR 606.120 and 121, 610.67 for requirements for blood products.

enhance the safe and effective use of prescription drug products and reduce the number of adverse reactions resulting from medication errors due to misunderstood or incorrectly applied drug information."[16]

The PLR format consists of three main elements:

- Highlights, a succinct description of the most important information for healthcare professionals;
- Table of contents; and
- Labeling details presented in numbered sections of the Full Prescribing Information (FPI).

Additionally, provisions of the 2006 rule that apply to all products, whether or not the prescribing information is required to follow PLR format, mandate that any FDA-approved patient labeling (such as a Medication Guide or Patient Package Insert) either accompany the prescribing information or be printed following the last section of the prescribing information.[16,31]

Labeling for any new prescription drugs and biologics' applications, and any that were approved since June 2001, must conform to the PLR (21 CFR 201.57) requirements (see **Table 5-3**[32]). However, as permitted by the PLR implementation plan, some older products still may carry prescribing information in the previous format, as described in 21 CFR 201.80.[31]

The PLR was one component of a broad FDA initiative to improve prescription medicine information for healthcare professionals. The agency also issued guidances to facilitate compliance with labeling regulations for most prescribing information sections to help sponsors develop labeling that will be useful to healthcare professionals.

Table 5-3. Required Sections of Prescribing Information for Drugs and Biologics in the US (PLR Format)[32]

Element	Sections	21 CFR 201.57
Highlights of Prescribing Information	Highlights limitation statement Drug names, dosage form, route of administration, controlled substance symbol (if needed) Initial US approval Boxed warning (if any) Recent major changes Indications and usage Dosage and administration Dosage forms and strengths Contraindications Warnings and precautions Adverse reactions Drug interactions Use in specific populations Patient counseling information statement Revision date	201.57(a)
Full Prescribing Information	Contents (table of contents)	201.57(b)
Full Prescribing Information	Boxed warning (if any)	201.57(c)(1)
	1 Indications and usage	201.57(c)(2)
	2 Dosage and administration	201.57(c)(3)
	3 Dosage forms and strengths	201.57(c)(4)
	4 Contraindications	201.57(c)(5)
	5 Warnings and precautions	201.57(c)(6)
	6 Adverse reactions	201.57(c)(7)
	7 Drug interactions	201.57(c)(8)
	8 Use in specific populations	201.57(c)(9)
	8.1 Pregnancy	201.57(c)(9)(i)
	8.2 Lactation	201.57(c)(9)(ii)
	8.3 Females and males of reproductive potential	201.57(c)(9)(iii)
	8.4 Pediatric use	201.57(c)(9)(iv)
	8.5 Geriatric use	201.57(c)(9)(v)
	9 Drug abuse and dependence	201.57(c)(10)
	9.1 Controlled substance (if scheduled)	201.57(c)(10)(i)
	9.2 Abuse	201.57(c)(10)(ii)
	9.3 Dependence	201.57(c)(10)(iii)
	10 Overdosage	201.57(c)(11)
	11 Description	201.57(c)(12)
	12 Clinical pharmacology	201.57(c)(13)(i)
	12.1 Mechanism of action	201.57(c)(13)(i)(A)
	12.2 Pharmacodynamics	201.57(c)(13)(i)(B)
	12.3 Pharmacokinetics	201.57(c)(13)(i)(C)
	13 Nonclinical toxicology	201.57(c)(14)
	13.1 Carcinogenesis, mutagenesis, impairment of fertility	201.57(c)(14)(i)
	13.2 Animal toxicology and/or pharmacology	201.57(c)(14)(ii)
	14 Clinical studies	201.57(c)(15)
	15 References	201.57(c)(16)
	16 How supplied/storage and handling	201.57(c)(17)
	17 Patient counseling information	201.57(c)(18)

Select guidances pertaining to the content and format of labeling for human prescription drug and biological products[33,34] include:

- Implementing the PLR Content and Format Requirements[31]
- Indications and Usage Section (Draft Guidance)[35]
- Dosage and Administration Section[36]
- Warnings and Precautions, Contraindications, and Boxed Warning Sections[37]
- Adverse Reactions Section[38]
- Clinical Pharmacology Section[39]
- Clinical Studies Section[40]
- Patient Counseling Section[41]
- Pregnancy, Lactation, and Reproductive Potential (Draft Guidance)[42,43]
- Pediatric Use Subsection[44]
- Geriatric Use Subsection[45]
- Immunogenicity Information (Draft Guidance)[46]

The FDA's website is the essential resource for labeling references material, including current guidelines and other information about the PLR. (See especially "Prescribing Information Resources" tab.)[47]

Highlights[31]

Generally, healthcare professionals saw the introduction of a Highlights section as likely to be helpful in navigating the lengthy and complex product labeling and recognizing the most critical product information. Manufacturers, however, expressed concerns about excluding important information, including context, to comply with the succinct format of the Highlights element. They felt it could diminish the communication of important information and be misleading, as well as create a basis for liability claims. Nevertheless, the FDA proceeded to require Highlights in the PLR format as being consistent with good risk communication practice and cognitive principles.[16]

The purpose of Highlights is to provide healthcare professionals immediate access to the most critical information in a concise summary and guide them to the details in the corresponding sections of the FPI. Highlights text is based on the FPI but should not be a verbatim repetition. Instead, it should consist of succinct statements describing the most relevant information in the FPI's first eight sections with recommendations for any necessary prescriber action. Each section of Highlights is followed by parenthetical references to the corresponding FPI section. Highlights are limited to one-half page; however, it is possible to obtain a waiver to permit a longer Highlights (e.g., for products with numerous indications or extensive warnings). The FDA requires a two-column format with ample white space to enhance communication.[16]

Once the text of each FPI section is established, the labeling development team can begin extracting the critical information for the corresponding section of Highlights. The time needed to create the concise, bulleted Highlights text should not be underestimated, given the difficulty of extracting each labeling section's essence using precise, succinct wording. Internal discussions about Highlights' content can be lengthy, iterative, and passionate.

"Recent Major Changes" appears under Highlights and identifies any substantial revisions only in the following sections during the preceding 12 months. This section includes the major headings for the revised sections, a parenthetical reference to the corresponding FPI section, and the month and year of the revision:

- Boxed Warning
- Indications and Usage
- Dosage and Administration
- Contraindications
- Warnings and Precautions

These changes are indicated in the FPI by a vertical line in the left margin next to the revised text. The information and corresponding vertical line in this section should be removed after one year (a small but significant task in maintaining up-to-date labeling).

Full Prescribing Information – Contents

The table of contents is numbered by FPI section heading. The table of contents does not include sections omitted from the FPI. In that case, the

heading "Full Prescribing Information: Contents" is marked with an asterisk corresponding to text at the end of Highlights stating, "Sections or subsections omitted from the full prescribing information are not listed." When a section or subsection is omitted, the numbering outlined in 21 CFR 201.56 should be maintained.

Full Prescribing Information (Select Sections)

Boxed Warnings

The FDA may require certain contraindications or serious warnings to be presented in a text box at the beginning of the FPI, especially those that may lead to death or serious injury or if there is a serious adverse reaction that can be prevented or reduced in frequency or severity. This boxed text provides a brief and concise summary of information critical for the prescriber to consider and refers to details included under Contraindications or Warnings and Precautions.

Contraindications

A drug is contraindicated in situations where the risk of use clearly outweighs the potential benefit. Only known hazards, and not theoretical possibilities, can be the basis for a contraindication. Contraindications can result from an observed adverse reaction or an anticipated adverse reaction, which is distinguishable from a theoretical possibility. Anticipated adverse reactions are supported by data.

Warnings and Precautions

Warnings and precautions include serious or otherwise clinically significant adverse reactions or other potential safety hazards, such as drug interactions or known risks for the pharmacologic class, steps to avoid them and actions to take if they occur. This section also describes any recommended monitoring and notes the potential for interference with laboratory tests.

Adverse Reactions

Another interesting feature of US formatting occurs with Section 6 Adverse Reactions. An adverse reaction is an undesirable effect reasonably associated with the use of a drug. This section does not include all adverse events observed, only those for which there is a basis for a causal relationship between the drug and the occurrence of the adverse event. This section begins with a description of a drug's overall adverse reaction profile on the entire safety database, followed by separate subsections:

- Clinical trial experience presents adverse reactions identified in clinical studies. Provide a description of the clinical trial data source; present a listing of common adverse reactions at or above a specified rate followed by a separate listing of less common adverse reactions. For adverse reactions with significant clinical implications, the listings must be supplemented by additional detail about the adverse reaction's nature, frequency, and severity.
- Immunogenicity information, if pertinent.
- Postmarketing experience lists adverse reactions identified from domestic and foreign spontaneous reporting. This listing must be separate from the listing of adverse reactions identified in the clinical trial experience.

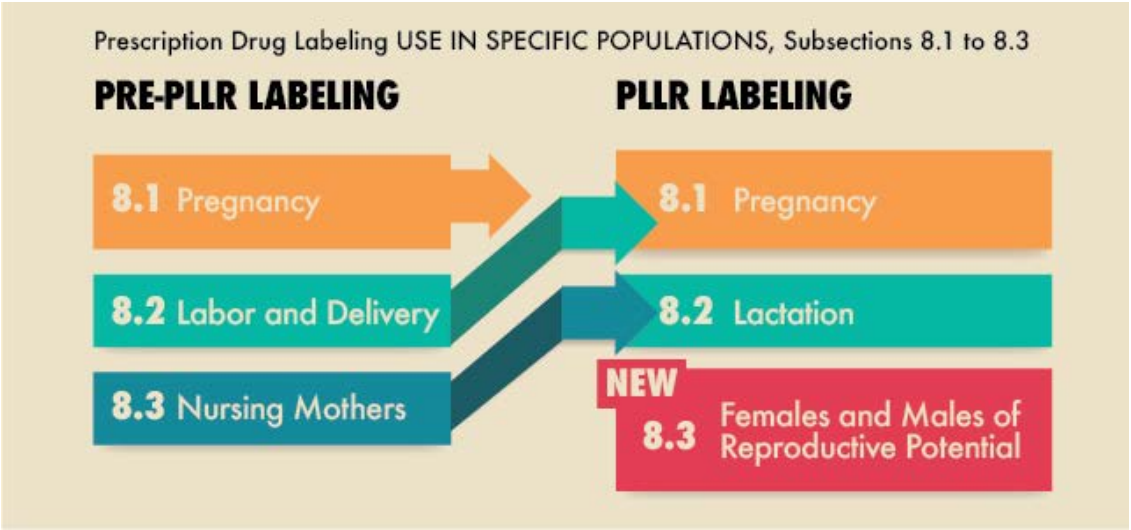
Pregnancy and Lactation Labeling Rule (PLLR)[42,43,48]

After a decade-long initiative and the issuance of a proposed rule in 2008, the FDA published the final Pregnancy and Lactation Labeling Rule (PLLR) in December 2014 for prescription drug and biologics' pregnancy and lactation labeling content and format. It also issued a guidance to facilitate compliance with the new requirements.

The PLLR redefined the content and reconfigured the format of these subsections in PLLR Section 8, Use in Specific Populations (see **Figure 5-1**[49]).

- The rule merged the previous Pregnancy and Labor and Delivery subsections into Pregnancy, which should include a summary of the risks of the drug during pregnancy, details of any pregnancy registries, and guidance to clinicians for decision making and counseling. Information in this

Figure 5-1. Prescription Drug Labeling Sections 8.1–8.3 (Use in Specific Populations)[49]



subsection is to be presented in the following order: Pregnancy Exposure Registry, Risk Summary, Clinical Considerations, and Data.

- Lactation replaced Nursing Mothers. This new subsection presents information relating to the presence of the drug in milk, effects on milk production, and risks to the breast-feeding child, along with recommendations on minimizing exposure and mitigating adverse effects. Information in this subsection is to be presented in the following order: Risk Summary, Clinical Considerations, and Data.
- The PLLR introduced a new subsection, Females and Males of Reproductive Potential, when necessary, to assist healthcare professionals in locating recommendations relating to pregnancy testing, contraception recommendations, and infertility information.

Both the Pregnancy and Lactation subsections should describe the underlying data.

Pregnancy categories (A, B, C, D, X) had been in use in prescription labeling since 1979 to convey distinctions in reproductive and developmental adverse effects in terms of available risk evidence. This system was limited in its ability to communicate distinctions among levels of risk, leading to confusion among healthcare professionals and misinterpretation for clinical decisions. The PLLR rule eliminated these categories in favor of a narrative structure for pregnancy labeling to describe drug exposure risks and the data on which the information is based to provide more meaningful information for healthcare providers.

Current and comprehensive information is available on the Pregnancy and Lactation Labeling (Drugs) Final Rule page on the FDA's website.[49]

Drug Abuse and Dependence

This section is included in the prescribing information of all medicines with a potential for abuse or dependence, not limited to those regulated under the Controlled Substances Act. If it is a drug controlled by the DEA, its schedule will be noted (e.g., Schedule II).

In a guidance issued for comment in July 2019,[50] the FDA noted the drug abuse and dependence section should concisely present information about "a drug's potential for abuse, misuse, addiction, physical dependence and tolerance" and for its safe and effective use in treatment. As specified in the regulations (21

CFR 201.57(c)(10)), the section will identify types of abuse that can occur and the adverse reactions associated with abuse, as well as "particularly susceptible patient populations." It also must describe characteristics of psychological and physical dependence, tolerance, and the effects of chronic abuse and abrupt withdrawal. The draft guidance highlights general labeling principles and recommends content (including terminology and definitions), organization of information, and how to avoid redundancy in other prescribing information sections.

Submissions and Review

New prescription product labeling is included in a new drug application (NDA)[51] or biologics license application (BLA)[52] in Module 1, Administrative Information – 1.14 Labeling. (With respect to the International Council for Harmonisation's [ICH] Common Technical Document [CTD], this is considered region-specific information.[53]) It can be argued that the entire dossier exists principally to support the manufacturing particulars and the product profile described in the labeling. As noted previously, all labeling content must be justified by evidence and annotated to the appropriate dossier components, whether in the summaries or overviews or within individual reports. To facilitate review, annotations should direct the reviewer to the specific table or section rather than simply to the relevant page in the supporting document.[52,54]

The labeling components are submitted in Extensible Markup Language (XML) format to meet Structured Product Labeling (SPL) requirements.[55] A sponsor also provides the FDA reviewing division with the manuscript of the prescribing information (and any required patient labeling) as an annotated PDF file, along with another copy in an editable format, such as MS Word. The PDF file will include live links from the labeling annotations directly to the source documents within the dossier to facilitate reviewer navigation. The Word manuscript, expunged of annotations, will be used as a working document for labeling negotiations between the FDA and the sponsor to track iterative proposals and counterproposals until all content is agreed.

Comments are usually received from the reviewing division approximately four to six weeks before the action date set by the Prescription Drug User Fee Act (PDUFA) for the submission, but comments or information requests can be requested at any time during the review process. Typically, the FDA regulatory project manager coordinates the provision of reviewer labeling comments to the sponsor. Depending on the regulatory project manager, comments and proposed changes may be collated and sent in a single document or staggered and sent as each reviewing discipline (e.g., clinical pharmacology, clinical, nonclinical toxicology, CMC) completes its review. For example, clinical pharmacology reviewers will send comments and proposed edits to text describing the active ingredient's mechanism of action, pharmacodynamics, and pharmacokinetics (Section 12), while feedback from the CMC reviewers will address chemical characterization, pharmaceutical particulars, and storage for the product and its constituents (Sections 11 and 16). Nonclinical reviewers will consider proposed text in the nonclinical toxicology section (13), as well as any discussion of animal data elsewhere in the labeling, such as text describing what is known about exposure during pregnancy and lactation (Sections 8.1 and 8.2). Clinical reviewers will share feedback on labeling content dealing with safety and efficacy, including the description of data from clinical trials and related directions and warnings for prescribers. They also will review the patient counseling section (17) and any patient labeling prepared by the sponsor, such as a Medication Guide.

While comments from the reviewing division will focus on translating the data for a benefit-risk assessment and provide guidance for use, the FDA's Labeling Policy Team will assess the labeling as a communication tool. They also review compliance with relevant guidances and policies, as well as consistency across therapeutic areas (reviewing divisions).[56]

Expedited Programs for Serious Conditions – Labeling Implications

The initial PDUFA in 1992 established the user fee model of review and performance goals for drug and biologic applications, including a category for priority reviews. Since then, other mechanisms have been introduced by legislative actions (Food and Drug Administration Modernization Act [FDAMA], Food and Drug Administration Safety and Innovation Act [FDASIA]) to facilitate patient access by expediting the development and review of new therapies: fast-track designation, breakthrough therapy designation, accelerated approval, and priority review designation.[57]

The standard practices of labeling development and review prevails under each program. However, the importance of reaching agreement over prescribing information and any patient labeling in the compressed timeframe associated with these programs underscores the advantage of developing target labeling early in the process (see Target Labeling chapter for more information).

Because the FDA may approve a product for a serious or life-threatening illness based on surrogate or intermediate endpoints using the accelerated approval pathway,[58] the agency issued a guidance to ensure that the prescribing information indications and usage section offers clear and complete information about the underlying clinical evidence, including limitations of usefulness and clinical benefit uncertainty. The guidance directs any confirmatory research to be highlighted in the indications section when a postmarketing study is required for approval. It also describes how the labeling is to be revised when clinical benefit has been verified or when an accelerated indication must be withdrawn.

Postapproval Labeling Revisions

Labeling is arguably the most dynamic regulatory document associated with drug development and maintenance, with hundreds of labeling changes made in the US each year.[59] A product's labeling will need frequent revision following the product's initial introduction, as it is used by a broader variety of patients than were exposed to it in controlled clinical settings, and when postapproval commitments include requirements for additional clinical research. The labeling also will reflect continuing sponsor development, such as research into additional indications and improved understanding about benefit-risk and usage revealed through continued safety monitoring. Further, it may be necessary to revise a product's labeling to comply with new regulations impacting product information or packaging. Revision frequency tends to diminish as products mature, shifting focus from enhanced usage to one of maintaining up-to-date safety information, pharmaceutical particulars, and regulatory compliance (see **Table 5-4**).

Revisions to FDA-approved drug and biologic labeling are submitted to the agency as supplements to the NDA or BLA. The type of submission depends on the nature of the changes. Refer to 21 CFR 314.70 (NDA) or 21 CFR 601.12 (BLA).[60-62]

Table 5-4. Some Reasons for Labeling Revision

New or expanded indications
Additional or modified dosing regimens
Changes to or addition of safety information
Addition or discontinuation of product strength, formulation, or packaging configuration
Change in the name or address of the manufacturer
Inclusion of class labeling statements
Compliance with new labeling requirements
Changes in international sourcing

- Prior Approval Supplement (PAS) is used for major changes that require submission and approval of a supplement before the product may be distributed with the revised labeling. This includes revisions to the Medication Guide or to any information required by regulations for the prescribing information (other than minor changes submitted in annual reports). For biologics, examples of this supplement type include labeling changes requiring completion of a study to demonstrate equivalence or changes in a cell line.[60,63,64]

Examples of PAS changes are addition of an indication, information to strengthen a claim, additional clinical or pharmacokinetic information, or revisions to the Highlights section.

The labeling components submitted with a PAS are the same as those included with NDA or BLA submissions (i.e., SPL)[55] along with a manuscript in an editable format, such as MS Word, showing the sponsor's proposed revisions to the currently approved labeling and a PDF file with annotations to supporting material. Labeling components, such as carton or container labels, not affected by the proposed change may be omitted from the submission. FDA review can take 6 to 10 months depending on the nature of the change and data submitted and can involve iterative negotiations to reach agreed wording for the revised labeling. Implementation for revised labeling submitted as a PAS must await FDA approval.

- Changes Being Effected (CBE) supplement is used for moderate changes. FDA approval is not required prior to implementation of the revised labeling. However, the FDA will issue an approval letter for a CBE supplement. Timeframe can vary.
    - CBE-30 submissions are used to make changes to CMC-related labeling content, such as those relating to the drug substance or drug product. The revised labeling may be implemented 30 days after submission.[60,65] Approval from the FDA may be received at any time following submission, often four to six months after filing.
    - CBE-0 submissions are intended for certain safety-related updates, such as the addition or strengthening of a contraindication, warning, precaution, or adverse reactions; statements about abuse and dependence; instruction about dosage and administration that is intended to increase the safe use; or deletion of false or misleading or unsupported claims of effectiveness. The revised labeling may be implemented immediately upon submission. This submission mechanism allows sponsors to comply with the requirement to revise labeling "…to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established."[60,65,66] Depending upon the nature of the change, the sponsor may wish to discuss the proposed change with the FDA's project manager prior to implementing the revised labeling for a CBE-0 submission to avoid the risk of the agency requiring significant changes following its review of the supporting data. The timing of formal FDA approval for such supplements will vary.

      The labeling components submitted with a CBE supplement are the same as those for other submissions, including SPL,[55] a manuscript marked with revisions to the currently approved labeling and an annotated PDF file, but will include copies of final printed labeling. Note that implementation without FDA approval may involve printing components at risk, since the FDA may require changes to the submitted and implemented labeling update. For this reason, such decisions will benefit from consultation with personnel responsible for managing packaging inventory so they may limit quantities until approval is granted.
- Safety change notification letters[67,68] – Section 505(o)(4) of the FD&C Act (added as the result of FDAAA Section 901) authorizes the FDA to require – and, if necessary, order – labeling changes for prescription products if it learns of new information about serious risks it determines should be included in the labeling. Previously, in the absence of such authority, negotiations with sponsors over agency-requested changes could be protracted. New safety information reflects a serious risk or unexpected serious risk associated with the drug that has been identified since approval. Revisions to boxed

warnings, contraindications, warnings and precautions, drug interactions, and adverse reactions (but not adverse reactions alone) are most common, but other sections may also be affected to ensure that all labeling for the product is consistent. Patient labeling also may be updated to include patient-oriented information about the new safety information. In addition, the FDA has the authority to require implementation of a Medication Guide if one does not currently exist.

Sponsors may respond to a safety change notification from the FDA by submitting a supplement with proposed labeling changes based on the new safety information. If the sponsor proposes revisions identical to those required in the safety change notification letter, the mechanism for submission should be a CBE-0. If not, the sponsor must submit a PAS with the proposed alternate labeling revisions. A sponsor also may disagree with the agency and respond by explaining why the change to the labeling is not warranted. Any supplement or rebuttal letter must be submitted to the FDA within 30 calendar days of receiving a safety change notification letter. For a PAS or rebuttal, the FDA may initiate a discussion period of no more than 30 calendar days, to be followed within 15 calendar days by approval of the supplement or a mandate to make the FDA-required changes.

- Annual report – Minor changes made to labeling over the previous period are described by the sponsor in an annual report. Examples of such changes may be in the description of the drug product, how it is supplied (unless it involves a change in the dosage strength or form), or editorial revisions.[60,69,70] The labeling may be implemented with these changes immediately. FDA approval is not given to annual report changes.

  Final printed labeling components are included with the annual report for the product, along with a description of the change(s).

Labeling for Generic Drugs

Generic drug products are the same as innovator products (listed drugs) if they are identical in their active ingredient(s), dosage form, strength, route of administration, and conditions of use (other than those indications under patent exclusivity).[71] Marketing authorization for these products will be based on the assurance of bioequivalence[72] through clinical data submitted in an abbreviated new drug application (ANDA), information about CMC,[73] and labeling that is identical to that of the listed drug information.[74] According to the FD&C Act, the ANDA must show:

> "…that the labeling proposed for the new drug is the same as the labeling approved for the listed drug…except for changes required because of differences approved under a petition…or because the new drug and the listed drug are produced or distributed by different manufacturers."[75]

The ANDA will include annotated draft versions of the prescribing information and any patient labeling for use with the generic product, as well as carton and container labels depicting content, format, and layout. It also will include the approved reference listed drug (RLD) labeling and side-by-side comparisons between the RLD labeling and that proposed for the generic, highlighting and explaining all differences.[74]

The generic labeling will be submitted electronically, with prescribing information and patient labeling in PDF, Word, and SPL formats. (It is no longer necessary to submit final printed labeling components with the ANDA.)[76]

Biosimilar Product Labeling

Biosimilar[77] products are derived from biological sources established as "highly similar" to the reference biologic by demonstrating there are no clinically meaningful differences in terms of product safety, purity, and potency.

As with generic drug products, biosimilar labeling is based on the prescribing information and any FDA-approved patient labeling for the reference product. However, biosimilar labeling will reflect relevant information from the reference

product labeling (RPL) consistent with the indications to be registered for the biosimilar product but will not necessarily use identical language as the reference biologic. This accounts for the natural variation in biologically sourced products, whereby the biosimilar labeling will include details relevant to the safe and effective use of that specific product, which may differ from that of the reference biologic. So, unlike generic drug labeling, which must be essentially identical to the RLD labeling, biosimilar labeling will be similar but is not expected to be identical. (Any Instructions for Use [IFU] of the biosimilar will incorporate relevant information from the reference product's IFU but will be modified to represent the biosimilar product's appropriate use.)

Information about the clinical research that provided evidence of the reference product's safety and effectiveness should be included in the biosimilar labeling. In contrast, the clinical studies conducted to demonstrate biosimilarity with the reference product generally should not be described in the labeling, as it is not helpful for prescribers.

Biosimilar product submissions will include the RPL, an annotated "tracked changes" manuscript for the biosimilar labeling highlighting and explaining differences from the RPL, and a clean proposed version of the biosimilar labeling manuscript.

Revisions to Generic Drug and Biosimilar Labeling

Due to the requirement to mirror the RLD labeling, when revisions are made to innovator product labeling, the generic product labeling needs to be updated as quickly as possible. While the FDA's Office of Generic Drugs had been alerting ANDA sponsors to changes, the onus for monitoring updates to RLD labeling has now shifted to the ANDA holder, who is then responsible for timely revision of the generic product's labeling consistent with that of the RLD.[75] (The link in the guidance is no longer maintained, so ANDA holders are expected to monitor Drugs@FDA[78] for updates to RLD labeling.)

Some safety issues that arise with the use of a generic version of a drug product may be related to the specific product marketed under the ANDA, such as excipients used in the final product formulation. However, evidence may point to risks associated with the therapeutic agent. In these cases, information should be shared with the RLD sponsor to determine whether a labeling change is warranted. The FDA, under the authority and mechanism discussed above, may require labeling revisions to the RLD (and thereby the labeling of all relevant generic products) for safety reasons.[67,68]

Even after the NDA for an RLD has been withdrawn for reasons other than safety or effectiveness, the ANDA holder retains the obligation to prevent the labeling of its generic version from becoming false or misleading as knowledge about the product advances. ANDA sponsors perform regular pharmacovigilance reviews of postmarketing data and have access to other, nonproprietary sources of relevant information, such as updates to the labeling of drugs in the same pharmacologic class and published literature, and may submit a PAS to revise their products' labeling.[79] Alternatively, under the authority and mechanism discussed above, the FDA may require labeling revisions to the labeling of all generic versions of a product without an active RLD.[67,68]

In 2013, the FDA proposed a rule[80] that would permit an ANDA holder to unilaterally implement a labeling revision for a generic drug for safety reasons, using a CBE-0 submission to the FDA and then sharing the revised labeling and justification sources with the RLD sponsor. The RLD sponsor would submit its own CBE-0 supplement with different changes if it disagreed with the ANDA holder's revisions. The FDA would review the submissions and approve a version of the labeling to be carried by all products, including those of other ANDA holders. The proposal met with vociferous industry opposition, particularly the generic industry. In December 2018, the FDA withdrew the proposal, citing challenges and unexpected consequences likely with its implementation, such as confusion among healthcare professionals owing to prolonged differences in labeling for brand and generic drugs. Notice of the withdrawal offered the FDA a chance to underscore generic

companies' and brand sponsors' obligations to ensure that their products' labeling does not become false, inaccurate, or misleading, stating, "If a generic drug maker becomes aware of new safety information that's not already in the drug label, they must also report it to the agency. This action, in turn, can result in safety changes that are directed by the FDA and would apply to all versions of the drug." Related initiatives and the FDA's commitment to play a proactive role in updating the labeling of older generic drugs were cited as the new approach for keeping labeling current throughout the product lifecycle.[81]

Labeling updates also are needed to reflect accruing information about biological products during their lifecycle. Biosimilar sponsors are responsible for pharmacovigilance of their products and updating labeling with new information to prevent it from becoming inaccurate, false, or misleading. Updates to the biosimilar labeling also could be prompted by expanded indications, either to catch up with the Reference Listed Biologic's (RLB's) original set of approved indications or to include a newly approved RLB indication. Changes in a biologic product's labeling during its lifecycle will create the need for updates to any biosimilar product's labeling for which it serves as a reference.[77]

Approval and Dissemination

Following negotiations for agreed labeling content, whether after initial NDA or BLA submission or as the result of revisions submitted in a supplement, the FDA will provide the sponsor with an approval letter (marked, for example, "NDA Approval" or "Supplement Approval") along with the final, approved version of labeling. (Examples of such letters can be found at Drugs@FDA.[78]) Sponsors should employ quality checks at each stage in the negotiation process, including carefully proofreading the final version delivered by the FDA.

The approval letter also will include instructions to submit the "content of labeling" (prescribing information) in SPL format. In December 2003, the FDA amended its regulations to require submission of all drug and biologic labeling in an electronic format. Following approval, the FDA requires the submission of the new prescribing information in SPL format to the drug establishment registration and labeling system, which then will transmit it to the National Library of Medicine for posting on the DailyMed website.[54,55]

The approved new or revised labeling should be expediently distributed within the sponsoring company to departments for which it serves as a critical reference, including pharmacovigilance for determining labeled and unlabeled adverse events, medical affairs for responding to product inquiries, and marketing departments for support of promotional activities. Company websites also should be updated with new or revised labeling when such websites display current product information. While there are no regulations regarding timelines for company website postings, it should be done in a timely manner. Company management should establish implementation timelines for its product labeling, including website posting as well as packaging printed inserts with products. The labeling development team must communicate with the manufacturing site to alert graphics and packaging engineers to an impending approval so printed labeling inventory can be appropriately managed.

Electronic Package Inserts (Paperless Labeling)

In the US, prescribing information still is required to physically accompany the product and is usually packaged with the carton or container. This situation arises from the provisions of FD&C Act Section 502 (f)(1), which declares[82] a drug is misbranded unless its label bears adequate directions for use, from which prescription medicines are exempted as long as "[l]abeling on or within the package from which the drug is to be dispensed bears adequate information for its use."[83]

In other words, in the US, the product received by pharmacists for dispensing must be accompanied by (packaged with) approved prescribing information. This situation persists, despite advances in information technology that support reliable electronic access to information, including drug information.

The requirement to package drugs and biologics with printed prescribing information also persists despite the pharmaceutical industry's long-term efforts to influence regulatory changes that would permit reliance on electronic labeling dissemination. The economic advantages of not having to maintain printed components and package them physically with their products are clear. Of potentially greater relevance to healthcare is eliminating outdated printed components.[84] Printed package inserts received at the pharmacy may be many weeks out of date due to the time required to print and package the components and to deliver inventory to dispensing sites. By contrast, electronic files can be updated rapidly, including correcting any errors, which may avoid recalls.

For more than a decade, beginning in the late 1990s, a Pharmaceutical Research and Manufacturers of America (PhRMA) task force representing industry, health professionals, the generic industry, and patients worked to assess practitioner readiness and consider various paperless models to support eliminating the requirement for printed prescribing information. (The initiative pointedly excepted patient labeling, which would continue to be packaged with the product.)

In 2014, the FDA issued a proposed rule on electronic distribution of prescribing information.[85] The proposal excluded emergency medicines, nonprescription drugs, and patient labeling. The report by the Government Accountability Office (GAO) on the study, prompted by FDASIA, found no consensus among stakeholders on the advantages and disadvantages of eliminating printed labeling. However, it is noteworthy that some of the concerns expressed in the report relate to the inclusion of patient labeling in the assessment's scope.[86]

In 2018, Congress – referring to the GAO report's "conclusions" that the proposal could adversely impact public health – forbid the FDA to use any funds to promulgate the rule.[87] Despite current congressional reluctance to move forward, the initiative to modernize prescribing information distribution has long-term viability.[88]

Pediatric Labeling

For the purposes of this section, *label* or *labeling* refers specifically to the prescribing information. The FDA implemented several initiatives to improve pediatric use information in drug labeling. Two regulations that were made permanent in 2012 under FDASIA were the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). The BPCA contains economic incentives for conducting pediatric studies, while PREA establishes requirements for studies of certain drugs and biologics in pediatric patients.

The sponsor must submit all data for inclusion in the labeling, which includes data submitted in response to a written request (per BPCA), a pediatric assessment in response to a study requirement (per PREA), or data required to fulfill an initial Pediatric Study Plan. Regardless of whether the data is positive, negative, or inconclusive, it must still be presented in the labeling. In addition, any safety concerns or lack of efficacy in a specific pediatric subpopulation must be included in the Pediatric Use section of the label. The Pediatric Use section is a subsection of Section 8 Use in Special Populations of the prescribing information. Information provided in this section may need to be divided into pediatric subpopulations, such as neonates, infants, children, and adolescents, depending on the data available that confirms the safety and efficacy in the pediatric population. As with all sections of the prescribing information, pediatric information must not be false or misleading. Additionally, the Pediatric Use section must include a regulatory statement, which is referred to as a Pediatric Use statement. This statement is required regardless of whether the drug or biologic is approved for the same indication in pediatric and adult patients or if the indication is different for pediatric and adult patients. The Pediatric Use statement should typically be the first sentence in the Pediatric Use subsection of the prescribing information.

Per the FDA guidance Pediatric Information Incorporated into Human Prescription Drug and Biological Product Labeling, dated March 2019,[44] there are four scenarios describing the

content of Pediatric Use information for the prescribing information:

1. Evidence supports the safe and effective use of the product in either all or specific pediatric subpopulations – indication.
2. Evidence does not support the safe and effective use of the product in either all or specific pediatric subpopulations – study negative or inconclusive – not indicated.
3. No evidence is available to support the safe and effective use of the product in either all or specific pediatric subpopulations – study not conducted or ongoing or the studies have been waived – not indicated.
4. Available evidence shows that the product is contraindicated for use in all pediatric populations or a specific pediatric subpopulation.

Depending on which scenario described above best fits the pediatric product information or data accumulated by the sponsor, the information or data may need to be included in additional sections of the prescribing information, such as indications and usage, dosage and administration, adverse reactions, clinical pharmacology, clinical studies, and contraindications (scenario #4 above).

Juvenile animal study data should be concisely summarized in the Pediatric Use subsection, under the heading Juvenile Animal Toxicity Data, after all of the other required data or information has been presented. The heading should reflect that the data is the juvenile animal study data and should only be included if a safety signal has been discovered that was not addressed previously. Sponsors should only include data that has clinical relevance. If the nonclinical and clinical data suggest a similar risk, the clinical data should be discussed in the Pediatric Use subsection, with a brief summary of the nonclinical data. The summary of juvenile animal study data should be discussed in clinically relevant terms, such as:

- Human equivalent dose exposures;
- Ages of animals and their correlation to human ages;
- Organ systems affected;
- Duration of treatment of animals and the relationship to clinical use;
- Reversibility of the adverse effect; and
- Developmental delay, if applicable.[44]

In general, there is no need to include a description of juvenile animal studies in the Nonclinical Toxicology section of the prescribing information.

Conclusion

Labeling for a drug or biologic is a critical source of information for healthcare professionals and patients because it is used to ensure the proper and safe use of the product. All labeling must be truthful and accurate and only contain information relevant to the indications for which the product is approved. The FDA continues to refine and update the required elements to be included in the prescribing information, such as introducing a subsection for immunogenicity under clinical pharmacology. All drug and biologic manufacturers, sponsors, or NDA/BLA holders must understand the labeling requirements for their specific products. Not all sections of the package insert are applicable to all drug and biologic products; for instance, the section on drug abuse and dependence is typically not relevant for biologics or biosimilars. Understanding the requirements will enable the creation of compliant labeling, which can decrease FDA comments and lead to faster final label approval.

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CHAPTER 6

Patient Labeling in the US

Cathleen O'Connell, PhD, MS, RPh,
Christine Holzmueller, and
Hoi Lam Chan, MPH, BPharm (Hons)

Evolution of Patient-Oriented Labeling for Prescription Medicines

Patient-oriented labeling for prescription medicines has been a compulsory standard in many countries for years. In contrast, there is no US requirement for sponsors to prepare and submit patient-oriented labeling for all prescription products for FDA review and approval, resulting in an inconsistent situation with respect to written drug information.

Beginning in the late 1960s, the FDA required labeling written in nontechnical language – Patient Package Inserts (PPI) – to be provided to patients with certain medicines, such as isoproterenol inhalers and products containing estrogen, to inform them of specific risks. In 1974, the agency initiated a project to investigate whether requirements for patient labeling should be expanded, based on the position that "…prescription drug labeling that is directed to patients will promote the safe and effective use of prescription drug products and that patients have a right to know about the benefits, risks, and directions for use of the products."[1] In 1980, the FDA issued a final rule to require manufacturers to provide a PPI for dispensing with new prescriptions. The initiative aimed to increase patient knowledge about the product and thereby encourage its optimal use. At the time, consumers were in favor of PPIs, but there was some opposition among healthcare professionals.[2] This regulation was withdrawn two years later as unnecessarily burdensome, costly, and contrary to requirements set forth in the 1981 Executive Presidential Order 12291 for promulgating new regulations.[3,4]

During the decade following withdrawal of requirements for sponsors to develop PPIs for all prescription products, the FDA periodically assessed the leaflets prepared by voluntary programs and found substantial variation in the written information's usefulness.[5] To align with the Public Health Service "Healthy People 2000" initiative's goals, the FDA published performance standards in 1995 for written patient drug information distribution and quality. At the same time, it proposed a regulation requiring patient labeling, specifically Medication Guides, for certain products that pose serious risk of harm "requiring immediate distribution of FDA-approved patient information."[3]

While the FDA was reviewing comments on the proposed rule on Medication Guides in 1996, Congress passed Public Law 104-180,[6] which formally established a voluntary private-sector initiative to develop a long-range action plan to meet the FDA's performance goals for both oral