CDER Forum for International Drug Regulatory Authorities

September 26, 2006

Labeling Overview

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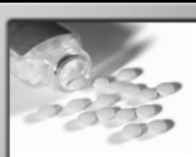
CDER Forum for International Drug Regulatory Authorities



Contents

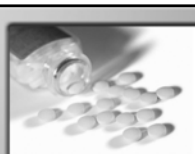
- Food Drug and Cosmetic Act
- What is Labeling?
- Labeling Requirements
- New Labeling: Content and Format
- Labeling Guidance
- How FDA Reviews/Approves Labeling
- FDA Labeling Initiatives

Food Drug and Cosmetic Act (FD & C Act)

- Gives authority to:
  - Interpret the law
  - Establish standards
  - Review and approve
  - Assure compliance
  - Enforce/protect

Brief History of FD&C Act

- 1906 Food and Drugs Act
  - Prohibited misbranding and adulteration of foods and drugs
- 1938 Federal Food Drug and Cosmetic Act
  - Pre-clearance of drugs for safety
- 1951 Durham-Humphrey Amendment
  - Separated prescription drugs from over-the-counter
  - Allowed FDA to regulate prescription drug labeling
- 1962 Kefauver Harris Amendment
  - Required drugs prove efficacy (in addition to safety)

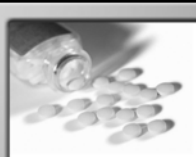


What is Labeling?

FD&C Act:

- "Label" is written, printed, or graphic matter on the immediate container of the drug product

- "Labeling" is all labels and other written, printed, or graphic matter accompanying such article the drug product



What is Labeling?

21 CFR 202.1 Prescription-drug advertisements

- Printed, audio or visual matter descriptive of a drug published for use by medical practitioners, pharmacists, or nurses supplied by the manufacturer, packer, or distributor are determined to be labeling as defined in the FD&C Act

Drug Labeling

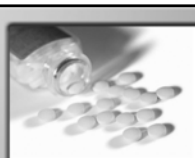
- Package insert (a.k.a. Professional Labeling)
  - Information that accompanies drug when drug is approved
- Other labeling
  - Patient Package Insert
  - Medication Guide
  - Brochures
  - Mail and letters
  - Bulletins
  - Calendars
  - Motion picture films
  - Sound recordings
  - Meeting exhibits and presentations
  - Medical literature

Regulated by Division of Drug Marketing, Advertising, and Communication (DDMAC)

Misbranding

FD&C ACT Section 502

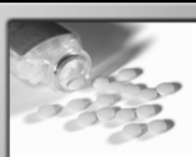
A drug product is misbranded if its “labeling is false or misleading in any particular [502(a)] ” and fails to have “adequate directions for use [502(f)].”



Labeling Requirements

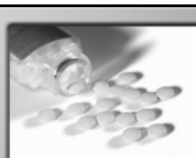
- Regulations describe the content and format requirements for labeling information
- 21 CFR 201.56 (General) and 201.57(Specific)
- Effective June 30, 2006, NEW 201.56 and 201.57 adopted for physician labeling rule (PLR)
- Most content requirements are maintained; significant format requirement changes

Final Rule: Requirements on the Content and Format of Labeling for Human Prescription Drug and Biological Products, January 24, 2006.
http://www.fda.gov/cder/regulatory/physLabel/default.htm



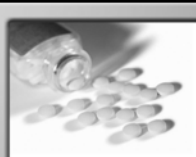
Goals for New Labeling Rule

- More informative labeling
- More accessible labeling
- Better risk communication
- Fewer medication errors



New 21 CFR 201.57 – Revised Labeling

- **Highlights**
  - High level ½ page summary
  - Links to appropriate section in FPI
  - "Information tool"
- **Contents**
  - Allows easy reference to FPI
  - Consistent order and numbering of sections
  - "Navigation tool"
- **Full prescribing information (FPI)**



Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Imdicon safely and effectively. See full prescribing information for Imdicon.

IMDICON® (cholinasol) CAPSULES
Initial U.S. Approval: 2000

WARNING: LIFE-THREATENING HEMATOLOGICAL ADVERSE REACTIONS

See full prescribing information for complete boxed warning.

Monitor for hematological adverse reactions every 2 weeks for first 3 months of treatment (5.2). Discontinue Imdicon immediately if any of the following occur:

- **Neutropenia/agranulocytosis (5.1)**
- **Thrombotic thrombocytopenic purpura (5.1)**
- **Aplastic anemia (5.1)**

----------RECENT MAJOR CHANGES----------

Indications and Usage, Coronary Stenting (1.2)	2/200X
Dosage and Administration, Coronary Stenting (2.2)	2/200X

----------INDICATIONS AND USAGE----------

Imdicon is an adenosine diphosphate (ADP) antagonist platelet aggregation inhibitor indicated for:

- Reducing the risk of thrombotic stroke in patients who have experienced stroke precursors or who have had a completed thrombotic stroke (1.1)
- Reducing the incidence of subacute coronary stent thrombosis, when used with aspirin (1.2)

Important limitations:

- For stroke, Imdicon should be reserved for patients who are intolerant of or allergic to aspirin or who have failed aspirin therapy (1.1)

----------DOSAGE AND ADMINISTRATION----------

- Stroke: 50 mg once daily with food. (2.1)
- Coronary Stenting: 50 mg once daily with food, with antiplatelet doses of aspirin, for up to 30 days following stent implantation (2.2)

Discontinue in renally impaired patients if hemorrhagic or hematopoietic problems are encountered (2.3, 8.6, 12.3)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 50 mg (3)

----------CONTRAINDICATIONS----------

- Hematopoietic disorders or a history of TTP or aplastic anemia (4)
- Hemostatic disorder or active bleeding (4)
- Severe hepatic impairment (4, 8.7)

----------WARNINGS AND PRECAUTIONS----------

- Neutropenia (2.4 % incidence; may occur suddenly; typically resolves within 1-2 weeks of discontinuation), thrombotic thrombocytopenic purpura (TTP), aplastic anemia, agranulocytosis, pancytopenia, leukemia, and thrombocytopenia can occur (5.1)
- Monitor for hematological adverse reactions every 2 weeks through the third month of treatment (5.2)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence >2%) are diarrhea, nausea, dyspepsia, rash, gastrointestinal pain, neutropenia, and purpura (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact (manufacturer) at (phone # and Web address) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- Anticoagulants: Discontinue prior to switching to Imdicon (5.3, 7.1)
- Phenytoin: Elevated phenytoin levels have been reported. Monitor levels. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Hepatic impairment: Dose may need adjustment. Contraindicated in severe hepatic disease (4, 8.7, 12.3)
- Renal impairment: Dose may need adjustment (2.3, 8.6, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 5/200X

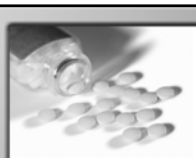


Table of Contents

FULL PRESCRIBING INFORMATION: CONTENTS*

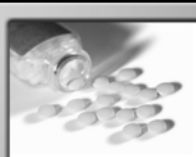
*Sections or subsections omitted from the full prescribing information are not listed.

Changes to Full Prescribing Information

- Warnings and Precautions consolidated into one section
- Formally in Precautions, now new sections
  - Drug Interactions
  - Use in Specific Populations
  - Patient Counseling Information
- Formally optional, now required
  - Clinical Studies
  - Nonclinical Toxicology
- Created Dosage Forms and Strengths section
- Moved How Supplied section to near end

Implementation Schedule

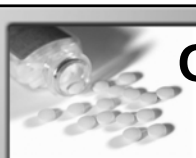
New NDA or efficacy supplement submitted:	**Label must conform:**
6/30/06 or after	At time of submission
Pending on 6/30/06 Approved 6/30/05-6/29/06	6/30/09 (3 years)
Approved 6/30/04-6/29/05	6/30/10
Approved 6/30/03-6/29/04	6/30/11
Approved 6/30/02-6/29/03	6/30/12
Approved 6/30/01-6/29/02	6/30/13
Approved Pre-6/30/01	Voluntary at any time (encouraged)



Companion Guidances

- Adverse Reactions Section of Labeling — Content and Format (Final)
- Clinical Studies Section of Labeling — Content and Format (Final)
- Implementing the New Content and Format Requirements (Draft)
- Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling — Content and Format (Draft)

http://www.fda.gov/cder/guidance/index.htm



Other Labeling Guidance Under Development

- Content and Format of Clinical Pharmacology Section of Labeling
- Content and Format of the Dosage and Administration Section of Labeling
- Drug Names and Dosage Forms
- Pharmacologic Classification for the Highlights of Labeling
- Target Product Profile

Guidance Agenda: Guidances CDER is Planning to Develop During Calendar Year 2006.
http://www.fda.gov/cder/guidance/CY06.pdf

How FDA Reviews/Approves Labeling

- Applicant (company) normally writes draft label
- Applicant submits draft labeling with supporting data (from clinical trials, animal studies) in NDA or BLA to FDA for review
- FDA reviewers determine appropriateness of draft labeling (internal meetings)
- Labeling negotiations with company
- Final labeling is approved by FDA once agreed to by FDA and applicant

Target Product Profile (TPP)

- FDA-PhRMA initiative (TPP Working Group)
- Template organized according to key sections in the product's labeling
- Sponsor completes the TPP template to identify the labeling concepts for drug development plan
- TPP submitted as a component of a briefing document and discussed at sponsor/FDA meetings
- Links each specific labeling concept to a specific study or other source of data that is intended to support the labeling concept

Drugs@FDA

- A Catalog of FDA Approved Drug Products
  - Approved and tentatively approved prescription, over-the-counter, and discontinued drugs
  - Searchable online database containing drug approval letters, labels, and review packages
  - Adobe Acrobat (.pdf) format

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Electronic Labeling Rule and Guidance

- December 2003 final regulations (the electronic labeling rule) require submission of the content of labeling in electronic format that FDA can process, review and archive
- Adopting new technology for processing and managing content of labeling submitted electronically
- Guidance describes how to submit the content of labeling using the Structured Product Labeling (SPL) standard, which is in extensible markup language (.xml) format

Guidance for Industry. Providing Regulatory Submissions in Electronic Format — Content of Labeling April 2005

Structured Product Labeling (SPL)

- The content of labeling in a standardized electronic file format with tagged blocks of text and coded data elements
- Use of this common format will enable all parties to create, send, and receive product labeling content
- Coded data elements will enable Decision Support Systems to develop query functions
  - » http://www.fda.gov/oc/datacouncil/SPL.html

DailyMed

- Managed by the National Library of Medicine
- Electronic repository of prescribing information
- Populated by current FDA labeling
- Comprehensive medication information for use in health care information systems
  - » http://dailymed.nlm.nih.gov/dailymed/about.cfm