



## NEW ERA IN US PRESCRIPTION DRUG LABELING

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### ABSTRACT

The overview of the paper is to give an idea of prescription drug labeling in United States. Prescription drug labeling helps in making labels more user friendly and which is an immediate and important source of medication information for patients. Although patients may obtain useful information from prescription drug labeling, its main purpose is to give healthcare professionals the information they need to prescribe drugs appropriately to the patients. FDA focused its effort on making labeling more informative and easy-to-read and minimize patient confusion and promote patient awareness on how to use a prescribed medicine safely and effectively, thereby reducing risk of medication error. The new drug labeling requirements was initially applied to recently approved prescription drugs and the drugs that received approval for new use, and later it was applied in gradually to other drugs. As per the new format, the prescription information for newly approved products must meet specific graphical requirements, including the reorganization of critical information so that physicians can find the information quickly. It may conclude in outlining the new format, which is helpful to understand exactly what a prescription drug labeling is in U.S.

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### INTRODUCTION

Pharmaceutical labeling/Drug labeling: It refers to all the printed information that accompanies a drug including the label, the wrapping and the packaging insert.

□ Drug labelling is regulated by the food and drug administration's division of drug marketing, advertising and communications.

□ These regulations apply to prescription drugs, over the counter drugs, and dietary supplements.

The term "labeling" according to the united states code 321(m) means all labels and other written, printed, or graphic matters(1) upon any article or any of its containers and wrappers or, (2) accompanying such article.

**Prescription drug labeling information is also known as<sup>1</sup>:**

- Prescribing information.
- Package inserts.
- Professional labeling.
- Direction circular.
- Package circular.

#### Importance of us prescription drug labeling:

According to the Institute of Medicine (IOM) 2006 report<sup>4</sup>, more than half a million adverse drug events (ADE's) occur in the United States each year. Problems with prescription drug (Rx) labeling were cited as the cause of a large proportion of patient medication errors and ADE's, as patients may unintentionally misuse a prescribed medicine due to improper understanding of instructions. 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.

#### Why more emphasis on the labeling???????

Over the years, prescription drug labeling was complex:

- Did not identify the approval date.
- Did not indicate whether there were any recent changes to the labeling.

- Made locating and using information difficult.
- Did not facilitate finding answers to specific questions.
- Eventually, in many cases, labeling lost its user focus.

It became a document to assure completeness for possible litigation instead of a source of easy-to-use medical information.

Generally a label should contain the following information about the following things<sup>1,4</sup>:

- A summary of essential scientific information for the safe and effective use of the drug.
- Must be informative and accurate.
- Use language that is not promotional in tone, false, or misleading.
- Not to make claims or suggest uses for drugs when there is no sufficient evidence of safety and a substantial evidence of effectiveness.
- Must contain information based on whenever possible data derived from human experience.
- The labelling must also be updated when new information becomes available.

#### And Hence the Patient's Preference was In the Following Manner<sup>1</sup>:

- Directions – Avoid vague terminology.
- Benefits of the medication (Indication).
- Warnings and possible side effects.
- Suggested responses to side effects (e.g., when to call doctor or stop taking medication).
- Duration of therapy.

FDA's goal for the prescription drug labelling<sup>4</sup> was to create a more useful risk-safety communication tool and to reduce errors caused by misunderstanding or incorrectly applied drug information.

- FDA focused its effort on making labelling more informative and easy-to-read

- In 1992 FDA conducted focus-group research to learn more about the problems with the old labelling.
  - Between 1993 and 1994, the agency conducted a national survey of physicians to gather additional information about how prescribers used labelling and what problems they had with it.
  - Emphasis on the problem associated with the labelling issues.
  - In order to implement a new regulation or change an existing one, FDA must obtain public comments and input on proposals.
  - Also must obtain the comments of the prescribers and seek the suggestions.
  - In 1995, FDA held a public meeting to discuss the prototype and received comments to the Federal Register notice announcing the meeting.
  - FDA analysed the comments and over the years worked with the pharmaceutical industry and others to revise the prototype and develop what would become the new labelling.
  - On December 22, 2000, the Proposed Rule for the labelling change was published in the Federal Register.
  - On January 24, 2006, the "Final Rule: Requirements on the Content and Format of Labelling for Human Prescription Drug and Biological Products" was issued.
- The products affected by the rule include applications for prescription drugs and biologics:
- ☐ Submitted to FDA on or after June 30, 2006
  - ☐ Approved by FDA 5 years prior to June 30, 2006
  - ☐ With major changes in the prescribing information approved five years prior to, on, or after June 30, 2006.
- The above said products shall follow the rules for the labeling requirements abide the labeling requirements.

#### **New labeling format:**

Basing the changes implemented by the FDA a new labeling format has been designed<sup>1</sup>.

- A. Adds Highlights section
- B. Adds Contents section
- C. Reorders and reorganizes sections
- D. Makes additional improvements

#### **A. HIGHLIGHTS SECTION:**

- ❖ This is perhaps the most significant change in the new labeling rule.
  - ❖ The very above said purpose was solved by incorporating the highlights.
  - ❖ The Highlights section was created because prescribers said they would use labeling more if it included a short, half-page synopsis.
  - ❖ It provides the overview of a drug's benefits and risks that healthcare professionals said was most important to them.
  - ❖ Highlight's section consists of information which is not repetitive but contains the concise summary of crucial prescribing information.
  - ❖ Essentially, the Highlights section is a brief one-half page summary of the more descriptive product labeling.
- The highlight section consists mainly of the following parts<sup>4</sup>:-
- Limitations Statement
  - Product Names and Date of Initial U.S. Approval
  - **Boxed Warning**
  - Recent Major Changes
  - **Indications and Usage**
  - **Dosage & Administration**
  - Dosage Forms & Strengths
  - **Contraindications**
  - **Warnings & Precautions**

➤ Adverse Reactions (listing of most common ARs)

➤ Drug Interactions

➤ Use in Specific Populations.

➤ Patient Counseling Information Statement.

One which are highlighted and in bold are Newly added section and one which is in italics and underlined contains critical prescribing information.

#### **AN EXAMPLE FOR 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 (cholinase) 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(5.1)
- Thrombotic thrombocytopenic purpura(5.1)
- Aplastic anaemia(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 sub acute 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, and 12.3)**

**-----DOSAGE FORMS AND STRENGTHS-----Capsules: 50 mg (3)**

#### **-----CONTRAINDICATIONS-----**

- Hematopoietic disorders or a history of TTP or aplastic anaemia (4)
- Haemostatic disorder or active bleeding (4)

- Severe hepatic impairment (4,8,7)

#### -----WARNING AND PRECAUTIONS-----

- Neutropenia (2.4% incidence; may occur suddenly; typically resolves within 1-2 weeks of discontinuation), thrombotic thrombocytopenic purpura (TTP), aplastic anaemia, agranulocytosis, pancytopenia, leukaemia, and thrombocytopenia can occur (5.1)
- Monitor for haematological 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](http://www.fda.gov/medwatch).**

#### -----DRUG INTERACTIONS-----

- Anticoagulants: Discontinue prior to switching to Imdicon (5.3, 7.3)
- Phenytoin: Elevated phenytoin in levels has 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)

❖The most important change made in the new type of labeling format includes:

#### **Boxed Warning:**

- The revised product labelling may contain boxed warning, also referred to as a Black-Box Warning.<sup>5</sup>
- The boxed warning in the Highlights section uses bullets for ease of reading and is limited to 20 lines.
- In the United States, a black box warning (also sometimes called a black label warning or boxed warning) is a type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects.
- It is so named for the black border that usually surrounds the text of the warning.
- The U.S. Food and Drug Administration(FDA) can require a pharmaceutical company to place a black box warning on the labeling of a prescription drug or in literature describing it when:
- The drug has serious adverse reactions.
- When a serious unwanted reaction can be prevented or can be reduced in frequency and severity.
- It is the strongest warning that the FDA requires.
- The FDA has required that black box warnings be placed on all antidepressant medications warning they may result in increased risk of suicidal tendencies in children and adolescents.
- FDA advisors have recommended Pfizer required to place a black box warning on their non-steroidal anti-inflammatory drug Celebrex (celecoxib) for cardiovascular and gastrointestinal risks.

#### MODEL EXAMPLE:

<p><b>WARNINGS</b></p> <p><b>LIVER WARNING:</b> This product contains acetaminophen, severe liver damage may occur if you take</p> <ul style="list-style-type: none"> <li>• More than 8 caplets in 24hours, which is the maximum daily amount.</li> <li>• With other containing acetaminophen</li> <li>• 3 or more alcoholic drinks every day while using this product.</li> </ul> <p><b>Do not use</b></p> <ul style="list-style-type: none"> <li>• With any other drug containing acetaminophen (prescription or non-prescription). If you are not sure whether a drug contains acetaminophen ask a doctor or pharmacist.</li> </ul>
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#### **B. FULL PRESCRIBING CONTENTS INFORMATION:**

➤Another format feature all prescription drug products will share is the new “Contents” section.

➤The Contents section addresses prescribers' concern “that it was difficult to use the old labeling format” to find specific information.

##### **1. Navigational Tool**

- To detailed safety information.
- To safety sections and subsections in the full prescribing information.

##### **2. Ease of Reference**

- Electronic hyperlinks to sections in the full prescribing information.

#### **C. REORDER AND REORGANIZE:**

The next and most important change made to the labeling includes re-ordering and re-organizing of the sections.

➤The "Indications and Usage" and the "Dosage and Administration" sections (information that healthcare professionals refer to most frequently and consider most important) are located at the beginning of the prescribing information.

➤Product identification information such as colour and scoring is located in both the "Dosage Forms and Strengths" and the "How Supplied" sections to preserve the *integrity* and *understanding* of both sections.

➤Next, the previous “Warnings and Precautions” sections were consolidated into one section that contains the most critical safety information.

➤Sections previously located in the Precautions section (Drug Interactions, Use in Specific Populations, and Patient Counselling Information) are now new sections in the labelling.

➤“Clinical Studies”, “Nonclinical Toxicology” “sections now required”.

➤The "Adverse Reactions" section follows the Warnings and Precautions section and consolidates (provides) risk information in one location

#### D. REVISION AND IMPROVEMENTS:

This section deals with revisions that have been made to the labeling:-

##### 1. Format requires

- Minimum 8-point font
- Tables and bullets
- Standardized bolding and white space

##### 2. Encourages Adverse Event Reporting, includes contact information

➤ Revisions were made to the safety information sections. Specifically, new changes can be seen in the "Contraindications" section, the "Warnings and Precautions" section, and the "Adverse Reactions" section.

##### Contraindications:

- Includes known hazards. i.e. Likelihood of occurrence and the size of population being affected.
- The statement ALLERGIC to specific component of the drug has been removed.

##### 3. Warnings and precautions section:

➤ Warnings and precautions have been made into one section and has been expanded to include the clinically significant adverse reactions.

##### 4. Clinically significant adverse reaction includes:

- Adverse reactions that require discontinuation, dose adjustment, or addition of another drug.
- Adverse reactions that significantly affect patient compliance.

##### 5. Adverse reactions:

- Covers a separate listing of adverse reactions that occurred during clinical trials and those that were reported after the drug was marketed.
- Adverse reactions from post-marketing clinical trials should be included with the clinical trial experience.
- Post-marketing spontaneous adverse reaction reports must be listed separately.
- No longer contains the extraneous events or laundry lists of adverse reactions.
- It will supplement with additional detail, the nature, severity, frequency of adverse reactions, and the relationship to dose and demographics.
- A toll-free number and Internet reporting information for suspected adverse events to encourage more widespread reporting of suspected side effects.
- In addition, a new *Patient Counseling Information* section places greater emphasis on the importance of communication between professionals and patients. The new section is designed to help doctors advise their patients about important uses and limitations of medications.
- If FDA has approved patient information for a prescription drug, it will be printed at the label immediately following the patient counseling information section or will accompany the label so it can be easily shared.

➤ As prescription information is updated in this new format it will be added to a new online health information clearing house called *Daily Med* that will provide up-to-date medication information free to consumers, healthcare professionals and healthcare information providers.

➤ In the future, this new information will also be provided through a website called [facts@fda.com](mailto:facts@fda.com), a comprehensive Internet resource designed to give one-step access for information about all FDA-regulated products.

##### Labelling Appearance:

➤ Generally covers how it should look, what is the font size and the appearance of the label are covered in this format.

➤ Font size of minimum 8 point with multiple formats including tables, bullets, bolding and spacing enhances visual and cognitive access to the drug information.

##### Languages to be used:

➤ All labeling information that is required by law or regulation must be in English.

➤ Only exception in U.S is Puerto Rico where different language. If the label or labeling contains any representation in a foreign language, all label information required under the FD&C Act must also appear in that language [21 CFR 701.2(b)]<sup>2</sup>.

##### What labeling information is required?

➤ The following information must appear on the principal display panel:

➤ An identity statement, indicating the nature and use of the product, by means of either the common or usual name, a descriptive name, a fanciful name understood by the public, or an illustration [21 CFR 701.11].

➤ An accurate statement of the net quantity of contents, in terms of weight, measure, numerical count or a combination of numerical count and weight or measure [21 CFR 701.13]<sup>2</sup>.

##### Conclusion:

➤ This article highlights the U.S revised prescription drug labeling which was region specific and this format made easy for patients for its effective use and convenient for doctors to prescribe as According to the Institute of Medicine (IOM) 2006 report, more than half a million adverse drug events (ADE's) occur in the United States each year. Problems with prescription drug (Rx) labeling were cited as the cause of a large proportion of patient medication errors and ADE's, as patients may unintentionally misuse a prescribed medicine due to improper understanding of instructions

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