



## Guidelines for Drug Package Inserts in India and United States: A Comparative Review

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### ABSTRACT

Package Inserts (PI's) are the printed leaflet that contains information based on regulatory guidelines for the safe and effective use of a drug. It is approved by the administrative licensing authority. Accurate and reliable drug information is essential for safe and effective use of marketed products. Regulatory requirements for drug PI or leaflets vary across nations. United States-Food and Drug administrative agencies amend their regulations governing the content and format of PI's from time to time. There is always a need to improve the format, content and language of the PI for better patient compliance, reducing preventable Adverse Drug Reactions, removing unnecessary healthcare economic burden, avoiding medication errors.

**Keywords:** Drug packaging, package inserts, India, United states, leaflet.

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### INTRODUCTION

Package insert (PI) is a document provided along with drug in its manufactured container. It is primary source of drug information to patient, containing details of pharmacokinetics and pharmacodynamics, adverse effects, overdose, drug interactions, special warnings and several other instructions related to drug. A good PI contains all the approved, essential, and accurate information required for safe and effective use of marketed products. It is written in a language that is not promotional, false or misleading. The evidence-based information should be updated regularly on PI. The reliable and specific information on PI helps the physician to know the safety and efficacy profile of medicine and reduce the medication errors.<sup>1</sup>

In a country like India, where physicians are overburdened with number of patients due to large population, the role of package insert becomes even more important. The information on PI is not only relevant to physicians and pharmacists but to the patients also. Various studies have concluded that PI can produce an important impact on patients compliance and thus on the ultimate effectiveness of drug use<sup>2,3</sup>. Looking at the importance of

PI for physician, pharmacist and patient, it is needed that regulatory agencies make the PI more user friendly and informative. The content, way of depicting the information and adherence of PI to recommended guidelines should be regularly monitored by regulatory agencies.

### National regulatory bodies in India and US

The Central Drugs Standard Control Organization (CDSCO) is the National regulatory authority in India. CDSCO works under the Ministry of Health and Family Welfare, Government of India. The CDSCO performs multiple operations in India to safeguard and promote public health by assuring safety, quality and efficacy of drugs, cosmetics and medical devices. The Drug Controller General of India (DCGI) is the chairperson governing all these operations.

CDSCO's equivalent counterpart in United States (US) is United States Food and Drug Administration (US FDA) which is responsible for regulating and supervising the safety of food, dietary supplements, drugs, vaccines, biological medical products, blood products, medical devices and cosmetics. It consists of an Office of Commissioner and four directorates overseeing the functioning of agency.

### Key documents for package insert labelling regulations

In India, the concept of package insert guidelines are regulated by the 'Drugs and Cosmetics Act (1940) and Rules (1945). Section 6.2 of Schedule D lists 8 parameters pertaining to therapeutic indications whereas section 6.3 indicates 8 parameters of pharmaceutical information (table 1). Section 6.2 mandates that the package insert must be in 'English'. Rule 96 and 97 provides guidelines for



labelling content and format of innermost and outermost container of drug.

The same guidelines in US comes under parts 201, 314 and 601 of Title 21 in Code of Federal Regulations (21 CFR pts

201, 314, 601)(4). CFR is a codification of the general and permanent rules published in the Federal Register by the Executive departments and agencies of the Federal Government. Title 21 of the CFR is reserved for rules of the Food and Drug Administration (table 1).<sup>4, 5</sup>

**Table 1:** Comparison of Indian Guidelines with US FDA Guidelines for PI

Indian CDSCO guidelines		US FDA guidelines
<b>Section 6.2: Therapeutic Indications</b>		<b>1. Highlights of prescribing information</b>
1	Posology and method of administration.	Product names, other required information
2	Contra-indications	Boxed warning
3	Special warnings and special precautions for use, if any.	Recent major changes
4	Interaction with other medicaments and other forms of interaction.	Indications and usage dosage and administration
5	Pregnancy and lactation, if contra-indicated.	Dosage forms and strengths
6	Effects on ability to drive and use machines, if contra-indicated	Contraindications
7	Undesirable effects/side effects.	Warnings and precautions
8	Antidote for overdosing	Adverse reactions
<b>Section 6.3: Pharmaceutical Information</b>		Drug interactions
		Use in specific populations
		<b>2. Full prescribing information: Contents</b>
9	List of excipients	<b>3. Full prescribing information</b>
10	Incompatibilities	Boxed warning
11	Shelf life in the medical product as packaged for sale	1. Indications and usage
12	Shelf life after dilution or reconstitution according to direction	2. Dosage and administration
13	Shelf life after first opening the container	3. Dosage forms and strengths
14	Special precautions for storage	4. Contraindications
15	Nature and specification of the container	5. Warnings and precautions
16	Instructions for use/handling	6. Adverse reactions
		7. Drug interactions
		8. Use in specific populations
		9. Drug abuse and dependence
		10. Overdosage
		11. Description
		12. Clinical pharmacology
		13. Nonclinical toxicology
		14. Clinical studies
		15. References
		16. How supplied/storage and handling
		17. Patient counseling information

### Amendments in package insert regulatory guidelines

Since 2000, there has been no amendments implemented in 'Drugs and Cosmetics Act (1940) and Rules (1945) sections 6.2, 6.3 but labelling manners of inner most container and every outer container of medicines were updated by amendments in rule 96 and 97.

**Table 2:** Drug label regulatory changes in India

<b>Amendment in labelling of medicines Rules 96 &amp; 97</b>	
Ministry of Health and Family Welfare G.S.R. 222 (E)	1. Name of the Drug (In the Drugs and Cosmetics Rules, 1945, in rule 96, in sub-rule (1), in clause (i), in sub-clause (A), for the portion beginning with the words "For this purpose" and ending with the words "name and shall be", the words.  (i) "For this purpose, the proper name of the drug or fixed dose combination drug other than fixed dose combinations of vitamin and other fixed dose combinations containing three or more drugs shall be printed or written in a conspicuous manner which shall be in the same font but at least two font size larger than the brand name or trade name, if any and In other cases, the brand name or the trade name, if any, shall be written in brackets below or after the proper name.
Ministry of Health and Family Welfare G.S.R. 408 (E).  For Scheduled G Drug	3. In the said rules, in rule 97, in sub-rule (1),— (i) for clauses (a) to (e), the following clauses shall be substituted, namely:—“(a) if it contains a drug substance specified in Schedule G, be labeled with following words in legible black coloured font size in completely red rectangular box.
Ministry of Health and Family Welfare G.S.R. 408 (E)  For Scheduled H Drug (CAUTION)	if it contains a drug substance specified in Schedule H and comes within the purview of the Narcotic Drugs and Psychotropic Substances Act, 1985 (61 of 1985) be labeled with symbol NRx, which shall be in red and conspicuously displayed on the left top corner of the label and shall also be labeled with the following words in legible black coloured font size in completely red rectangular box.
Ministry of Health and Family Welfare G.S.R. 408 (E).  For Scheduled H Drug (Warning)	if it contains a drug substance specified in Schedule X, be labeled with symbol XRx, which shall be in red and conspicuously displayed on the left top corner of the label and shall also be labeled with the following words in legible black coloured font size in completely red rectangular box.
Ministry of Health and Family Welfare G.S.R. 408 (E)  For Scheduled X Drug	if it contains a drug substance specified in Schedule H1, be labeled with symbol Rx, which shall be in red and conspicuously displayed on the left top corner of the label and shall also be labeled with the following words in legible black coloured font size in completely red rectangular box.
Ministry of Health and Family Welfare G.S.R. 408 (E)  SCHEDULE H 1 PRESCRIPTION DRUG (CAUTION)	if it contains a drug substance specified in Schedule H1 and comes within the purview of the Narcotic Drugs and Psychotropic Substances Act, 1985 (61 of 1985) be labeled with symbol NRx, which shall be in red and conspicuously displayed on the left top corner of the label and shall also be labeled with the following words in legible black coloured font size in completely red rectangular box.

### Amendments in US Package Insert regulatory guidelines

The PI culture in US started in 1968 with a 2-line warning on PI of isoproterenol. Since then, several changes have been implemented in package insert format and the content, but lately FDA acknowledged that the content included in the PI had become lengthy, detailed, and complex, hence it was difficult for health practitioners to locate a specific information<sup>6</sup>.

To address this problem, FDA proposed a new format of PI in 2000 and, after public meetings and comment by practitioners, a final version became official in 2006. The aim of new PI format was to reduce medication error and save physicians time to find the required information, also

the new format can help reduce ADR happening due to medication errors. Preventable adverse drug reactions (ADR) occur at a rate of 400,000 per year according to a Institute of Medicine (IOM) study and costs 3.5 billion US Dollar<sup>7</sup>.

The FDA developed a new package insert format that has three major sections: (Figure 1,2)<sup>8</sup>

- (1) The Highlights of Prescribing Information: Highlights the clinically relevant information to physicians.
- (2) Full Prescribing Information Table of Contents: Lists all the contents of PI.
- (3) The Full Prescribing Information (FPI): Explains all the contents of section 2 in details.



**Figure 1: The Highlights of Prescribing Information**

<b>HIGHLIGHTS OF PRESCRIBING INFORMATION</b>	
These highlights do not include all the information needed to use Imdicon safely and effectively. See full prescribing information for Imdicon.	
<b>IMDICON® (cholinolol) CAPSULES</b> Initial U.S. Approval: 2000	
<b>WARNING: LIFE-THREATENING HEMATOLOGICAL ADVERSE REACTIONS</b> <i>See full prescribing information for complete boxed warning.</i> 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:	
<ul style="list-style-type: none"> <li>• Neutropenia/agranulocytosis (5.1)</li> <li>• Thrombotic thrombocytopenic purpura (5.1)</li> <li>• Aplastic anemia (5.1)</li> </ul>	
<b>RECENT MAJOR CHANGES</b>	
Indications and Usage, Coronary Stenting (1.2)	2/200X
Dosage and Administration, Coronary Stenting (2.2)	2/200X
<b>INDICATIONS AND USAGE</b>	
Imdicon is an adenosine diphosphate (ADP) antagonist platelet aggregation inhibitor indicated for:	
<ul style="list-style-type: none"> <li>• Reducing the risk of thrombotic stroke in patients who have experienced stroke precursors or who have had a completed thrombotic stroke (1.1)</li> <li>• Reducing the incidence of subacute coronary stent thrombosis, when used with aspirin (1.2)</li> </ul>	
Important limitations:	
<ul style="list-style-type: none"> <li>• For stroke, Imdicon should be reserved for patients who are intolerant of or allergic to aspirin or who have failed aspirin therapy (1.1)</li> </ul>	
<b>DOSAGE AND ADMINISTRATION</b>	
<ul style="list-style-type: none"> <li>• Stroke: 50 mg once daily with food. (2.1)</li> <li>• Coronary Stenting: 50 mg once daily with food, with antiplatelet doses of aspirin, for up to 30 days following stent implantation (2.2)</li> </ul>	
Discontinue in renally impaired patients if hemorrhagic or hematopoietic problems are encountered (2.3, 8.6, 12.3)	
<b>DOSAGE FORMS AND STRENGTHS</b>	
Capsules: 50 mg (3)	
<b>CONTRAINDICATIONS</b>	
<ul style="list-style-type: none"> <li>• Hematopoietic disorders or a history of TTP or aplastic anemia (4)</li> <li>• Hemostatic disorder or active bleeding (4)</li> <li>• Severe hepatic impairment (4, 8.7)</li> </ul>	
<b>WARNINGS AND PRECAUTIONS</b>	
<ul style="list-style-type: none"> <li>• 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)</li> <li>• Monitor for hematological adverse reactions every 2 weeks through the third month of treatment (5.2)</li> </ul>	
<b>ADVERSE REACTIONS</b>	
Most common adverse reactions (incidence >2%) are diarrhea, nausea, dyspepsia, rash, gastrointestinal pain, neutropenia, and purpura (6.1).	
<b>To report SUSPECTED ADVERSE REACTIONS, contact (manufacturer) at (phone # and Web address) or FDA at 1-800-FDA-1088 or <a href="http://www.fda.gov/medwatch">www.fda.gov/medwatch</a>.</b>	
<b>DRUG INTERACTIONS</b>	
<ul style="list-style-type: none"> <li>• Anticoagulants: Discontinue prior to switching to Imdicon (5.3, 7.1)</li> <li>• Phenytoin: Elevated phenytoin levels have been reported. Monitor levels. (7.2)</li> </ul>	
<b>USE IN SPECIFIC POPULATIONS</b>	
<ul style="list-style-type: none"> <li>• Hepatic impairment: Dose may need adjustment. Contraindicated in severe hepatic disease (4, 8.7, 12.3)</li> <li>• Renal impairment: Dose may need adjustment (2.3, 8.6, 12.3)</li> </ul>	
<b>See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling</b>	

**Figure 2: Full Prescribing Information Table of Contents****FULL PRESCRIBING INFORMATION: CONTENTS\*****WARNING – LIFE-THREATENING HEMATOLOGICAL ADVERSE REACTIONS****1 INDICATIONS AND USAGE**

- 1.1 Thrombotic Stroke
- 1.2 Coronary Stenting

**2 DOSAGE AND ADMINISTRATION**

- 2.1 Thrombotic Stroke
- 2.2 Coronary Stenting
- 2.3 Renally Impaired Patients

**3 DOSAGE FORMS AND STRENGTHS****4 CONTRAINDICATIONS****5 WARNINGS AND PRECAUTIONS**

- 5.1 Hematological Adverse Reactions
- 5.2 Monitoring for Hematological Adverse Reactions
- 5.3 Anticoagulant Drugs
- 5.4 Bleeding Precautions
- 5.5 Monitoring: Liver Function Tests

**6 ADVERSE REACTIONS**

- 6.1 Clinical Studies Experience
- 6.2 Postmarketing Experience

**7 DRUG INTERACTIONS**

- 7.1 Anticoagulant Drugs
- 7.2 Phenytoin
- 7.3 Antipyrene and Other Drugs Metabolized Hepatically
- 7.4 Aspirin and Other Non-Steroidal Anti-Inflammatory Drugs
- 7.5 Cimetidine
- 7.6 Theophylline
- 7.7 Propranolol
- 7.8 Antacids
- 7.9 Digoxin
- 7.10 Phenobarbital
- 7.11 Other Concomitant Drug Therapy
- 7.12 Food Interaction

**8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

**10 OVERDOSAGE****11 DESCRIPTION****12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

**13 NONCLINICAL TOXICOLOGY**

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

**14 CLINICAL STUDIES**

- 14.1 Thrombotic Stroke
- 14.2 Coronary Stenting

**16 HOW SUPPLIED/STORAGE AND HANDLING****17 PATIENT COUNSELING INFORMATION**

- 17.1 Importance of Monitoring
- 17.2 Bleeding
- 17.3 Hematological Adverse Reactions
- 17.4 FDA-Approved Patient Labeling

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

**The changes needed in Indian Package insert Guidelines**

India is a country with enormous variations in demographic characteristics of patients and several languages. The education levels of patients differ from one another. However, with increasing levels of literacy, the patients are becoming more aware about their own health and safety

issues and they try to find such information on internet and on package inserts as well but on the other hand there are area where patients of low socioeconomic status and low literacy rate still rely solely on medication information provided by physician. The role of PI becomes even more significant in such cases. The Indian package insert format has not been simplified yet like US Package insert. The



information present on PIs is so tedious and vast that it is not always possible for physician to extract the specific information out of it. If we compare Indian PI with US, we find the US format is cleaner, easy to understand and more informative. The highlighted information is mentioned right on the first page with various typographical enhancements, this saves the physician time to extract information. The important information like 'Box Warning', indications, ADR's, contraindications etc. are highlighted with special emphasis on way of presentation.

The US FDA along with 2006 amendments in PI Format, also released guidance document on how to make the PI information more visually impactful to reader. It recommends using special fonts, underlining information, box enclosure, putting marginal vertical lines, using different font sizes for headings and bolding them. The Indian package inserts are yet to follow these recommendations. However, Indian PIs use some of these key features to prioritize the information but it is not uniform and mandatory<sup>5</sup>.

The Indian package inserts need to be more patient oriented following the international recommendations. PIs in Europe and US have subsections devoted to patient information explaining safety and instructions of use in non-technical language whereas Indian PI mentions no such information. Last subsection of US PIs i.e. patient counselling information, advises patients about diet, lifestyle changes, side effects, directions to use.

India is diverse country in terms of population and languages; however, English is considered as standard language of communication in many ways but not everyone is educated enough to understand it. Probably multilingual format of PI will help in reaching out to a greater number of patients as information will be disseminated in understandable languages, which the patients are expected to understand the best. The multilingual formats of PIs are already in use in Europe and implementation of same in India can be a big help to poorly educated patients<sup>9</sup>. The Drugs Technical Advisory Board (DTAB) recently in April 2019 in their 82<sup>nd</sup> meeting recommended that government procurement agencies should take necessary steps in the tendering process to include the regional language, along with English, on the label of iron tablets and polio drops in government programmes.<sup>10</sup>

There is no electronic database of PIs in India like US and Europe. In US the drug information is available for reference as 'Prescribers' Digital Reference' accessible on [www.pdr.net](http://www.pdr.net).<sup>11</sup> It is a free drug research tool indicating all the PI information. Electronic databank not only saves the time of physician but also provide convenience of accessing the information anytime by browsing internet.

#### Future aspect: the road ahead

India is now among the top five pharmaceutical emerging

markets of the world and 3<sup>rd</sup> largest producer of medicines in terms of volume<sup>12</sup> and this trend is going to go up even further with increasing need of medications with rising population. Establishing electronic central data base of drug information looks more like a necessity rather than convenience. Patients compliance, reducing preventable ADR's, removing unnecessary healthcare economic burden, avoiding medication errors all these are easily achievable just by enhancing the quality of PIs.

#### CONCLUSION

Comparing Indian PI guidelines with US, we found there are various modifications and improvements required in Indian guidelines as well. There is need to improve the format, content and language of the PI in India. Implementations of typographical emphasis markings will be commendable as it will generate impact on reader and information will be easier to extract. The pharmaceutical companies shall be more stringent in providing all the information demanded by guidelines. The PI should be optimized and tested before marketing by regulatory bodies for lack of information. The government should ensure pharmaceutical companies are complying with the current regulations. CDSCO should invite suggestions from physicians to help improve the format of PI's.

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