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REVIEW ARTICLE

Regulatory Requirements for Packaging and Labeling of Pharmaceuticals in India and USA

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ABSTRACT

In pharma industry Packaging and Labeling plays very important role for improvements of attraction to human beings. This study provides an overview of regulatory requirements and tests for Quality control and suitability of packaging and labeling of prescription and Over-The-Counter (OTC) Products in USA and India. The study had been in formative to understand the need and importance of the labeling requirements of pharmaceuticals to protect the consumers by providing the suitable instructions for the use of the drug product at suitable place and suitable format. Guidance provides the recommendations for submission.

KEYWORDS

Innovator, Generics, PLR (Physician Labeling Rule), OTC, FPL (Final Printed Labeling), Testing of packages, ANDA, Regulatory requirements, USA, India Market

OBJECTIVE

The study encompasses the regulatory requirements for packaging and labelling of prescription drugs and Over-The-Counter products in United States of America (USA) and India.

- To study the regulatory requirements for packaging and labelling of pharmaceuticals in India and USA
- To study the special type packaging requirements, such as child resistant packaging and tamper evident packaging.
- To study the revision of Abbreviated New Drug Application (ANDA) labelling according to the Reference Listed Drug (RLD) labelling. Side by side comparison of labelling of PREVACID (Innovator) and Lansoprazole delayed capsules (Generic manufacturer).

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The main objective is to make improvements to medicines labelling and packaging within the current regulatory framework and as per the guidances which will add clarity to the information provided, assist healthcare professionals and patients/carers to select the correct medicine and use it safely, thereby helping to minimise medication errors.

INTRODUCTION

The safe use of all medicines depends on users reading the labeling and packaging carefully and accurately and being able to assimilate and act on the information presented. The primary purpose of medicines labeling and packaging should be the clear unambiguous identification of the medicine and the conditions for its safe use. Common factors affecting all users of medicines may be summarized under three headings:

Information

Certain items of information are vital for the safe use of the medicine.

Format

The information must be presented in a legible manner that is easily understood by all those involved in the supply and use of the medicine.

Style

There is potential for confusion between both similarity in drug names and similarity in medicines packaging.

Packaging is a combination of science, art and technology. Packaging is defined as the collection of different components which surrounds the pharmaceutical product from the time of production to use. It is an important constituent of medicinal products as it guarantees the product stability and integrity. Packaging became a very important tool for marketing a product.

The first impression is the last impression. Packaging plays a very important role in creating that impression for any product. But when it comes to pharmaceuticals, it has to go beyond looks. The success and failure of any product depend on how they are presented to the end users, especially if it is a medicine.

Certainly, packaging and labeling plays an important role in health care domain. Packaging can be divided into categories, like: Primary container, critical secondary container, secondary container, additional packaging, unit of sale and final exterior packaging etc. There are a few regulatory requirements to be fulfilled for packaging operation like suitability, safety, protection, compatibility, Quality Control, and stability.

Labeling refers to all the printed information which accompanies with the drug, including the label, wrapping and packaging insert etc. According to the Federal Food, Drug, and Cosmetic Act - Labeling means all labels and other written, printed, or graphic matters upon any article or any of its containers or wrappers, or accompanying such article. The primary purpose of the labeling is to make identification of the product clear and unambiguous. Labeling information is important for both healthcare professionals and patients. Once the product comes out of the pharmacy, the only source of communication the manufacturer has with the patient is packaging. So the information on the pack must be consistent and it should ensure the safe use of medication[6].

Label must provide accurate and clear instructions to the medical practitioners and consumers. Labeling is required to contain all the details of ingredients. It must describe the uses, directions of usage and contraindications of medicinal product. Prescription drug labeling contains three sections includes highlights of prescribing information, contents and full prescribing information.

The safe use of medicine depends on the presentation of the information by manufacturer and understanding the same by the practitioner and user

Drugs need more protection from tampering as if tampering occurs it results in the change in the drug that leads to failure to cure illness or even death of the patient. So the manufacturers of over-the-counter (OTC) products have the responsibility to protect the medicine as well as the patient.

By considering all the factors affecting the safe use of medicines regulatory agencies came out with a law and recommendations in the form of guidance for those involved in design of labeling and packaging components. And the person involved in the operation should ensure.

Research Methodology

The methodology involves collection of information related to prescription and Over The Counter (OTC) pharmaceutical products packaging and labeling, regulatory requirements, revision of Abbreviated New Drug Application (ANDA) labeling according to Reference Listed Drug (RLD) labeling, various labels of pharmaceuticals and study of these regulatory requirements.

Data Collection

Major part of the information is collected from primary sources. This information is the main source of study.

Primary Source

Primary source of information for the project is internet database. The United States Food and Drug Administration (USFDA) guidelines, code of federal regulations (CFR), United States Pharmacopoeia (USP), Central Drugs Standard Control Organization (CDSCO) guidelines, Drugs and Cosmetics Act 1940, and Rules, Indian Pharmacopoeia (IP). The above mentioned guidelines and information was collected majorly from the following websites:

1. United States Food and Drug Administration (USFDA) www.fda.gov

2. Central Drugs Standard Control Organization (CDSCO) www.cdsco.nic.in

Secondary Source

Secondary source of information include the knowledge gained by interaction with industrial professionals in Regulatory Affairs department, Packaging R&D department, this knowledge has helped me in the study of the requirements and side by side comparison of ANDA labeling and RLD labeling.

Packaging and Labeling Requirements for USA

Packaging System

Packaging system composed of container and closure. It may also include several layers of protection for the pharmacopoeial preparation along with any sealing device, delivery device and labeling and packaging inserts.

Primary Container

Primary container is the component of packaging system that maintains the direct contact with the product. This is to protect the product from environmental hazards during shipping and handling.

Secondary Container

Secondary container is which encloses one or more primary containers. It is used to carry the required label and also to hold the primary container together with the delivery device or other add-on feature. This also provides the protection to the components during the handling.

Container for pharmaceutical use is an article which holds or intended to contain and protect the drug. This may be in direct contact with the product. Closure is a part of container.

Packaging Material

Any material including printed material, employed in the packaging of pharmaceutical product excluding any outer package used for transport or shipment.

Packaging Information to be provided in the Submission

The information included in the application should be enough to provide the evidence that the container closure system and its components are suitable for its intended use.

Type and detailing of the information depends on the dosage form and its route of administration, unlike liquid orals solid orals are in less contact with the container closure system. So, the information provided in the application for liquid preparations should contain more detailed than solid oral preparations.

A detailed description about the container closure system should be included in the Chemistry, Manufacturing and Controls (CMC) section of application. Along with this the given information should be provided by applicant for each individual component of packaging system.

a) Identification by product name, product code (if available), the name and address of the manufacturer, and a physical description of the packaging component such as, type, size, shape, and color.

b) Identification of the materials of construction should be identified by a specific product designation (code name and/or code number) and the source (name of the manufacturer). Alternate materials of construction should also be indicated. Recycled plastic is not acceptable for preparing primary component. If it is used in secondary component the justification for its quality attributes should be provided.

c) Description of any operations or preparations that are performed on a packaging component by the applicant (such as washing, coating, sterilization, or depyrogenation) should be included.

d) To ensure the safety and post approval consistency in safety, the complete chemical composition of each material used in packaging system should be provided.

e) Different types of test are required to perform to qualify and characterize the material. The complete description about the test methods, acceptance criteria, reference standards and test results should be provided.

f) To address safety and compatibility, the results of extraction/toxicological evaluation studies should be provided for drug products that are likely to interact with the packaging components and introduce extracted substances into the patient.

g) Stability study of the drug product in the proposed container closure system should be conducted. The container closure system should be clearly identified in the study protocol. The container closure system should be monitored for signs of instability. The evaluation of packaging system should be included in the protocol and the observations, results and any corrective actions should be included in the stability report.

h) Generally tests provided in pharmacopoeia are sufficient for establishing the characteristics of the particular material. If any non-pharmacopoeial method is used, applicant should provide justification for the use of the test, a complete and detailed description of how the test was performed, and an explanation of what the test is intended to establish.

i) If any equivalent method available in the pharmacopeia, comparative data and the supporting data for the suitability of the method should be provided.

Suitability of the Container Closure System

Suitability refers to the ability of the container closure system to work according to its intended use.

- It should adequately protect the dosage form,
- It should be compatible with the dosage form,
- It should be composed of materials that are considered safe for use with the dosage form and the route of administration.
- If the packaging system has a performance feature in addition to containing the product, the assembled container closure system should be shown to function properly.

A container closure system should provide the dosage form with adequate protection from factors that can cause degradation in the quality of that dosage form during its shelf life. Common causes of such degradation are: exposure to light, loss of solvent, exposure to reactive gases (e.g., oxygen), absorption of water vapor, and microbial contamination

Packaging components which are compatible with the drug substance or product packed in it, will not interact sufficiently to cause unacceptable changes to the quality of either product or packing material. The construction material should not leach any undesirable materials to which the patient will be exposed when treated with the drug product. This is specially considered in case of materials which are in direct contact with the product, it is also taken into consideration in such a case where the material may migrates into the product. In case of parenterals, opthalmics, and inhalations an extensive study of the construction material is necessary. This involves the extraction study to know the type of chemicals that will migrate from the material into dosage form and toxicology study to know the effect of the substance and determine its safety levels.

The information related to suitability such as, description of tests, methods, acceptance criteria, reference standards, and validation information for the studies should be provided in the application. The information should be submitted directly in application or indirectly by

referencing to a Drug Master File (DMF). If it is referenced to a DMF, a letter of authorization must be submitted along with application.

Quality Control of Packing Components

The application should contain the information related to the quality control measures taken to ensure the quality of the components. These quality control measures are required to ensure the consistency in the quality after the approval. Majority of considerations are given to physical and chemical attributes.

Variation in the physical parameters considered important if it can affect the quality of the dosage form. Chemical composition may change affect the safety of the packaging component. Any change in the composition may result in extraction of new chemicals or change in the quantity of the extract.

Secondary packaging components give the additional protection to the dosage form. Such as, protection from light, protection from excessive solvent loss protects from excessive moisture and reactive gases permeation, protection from rough handling and protect from microbial contamination. In the application very less information should be provided about secondary packaging components as they were not in direct contact with the dosage form[11].

Tables 1, 2 & 3 provide the information need to be submitted in the application for various dosage forms.

Table1: Regulatory information to be submitted in an original application for any drug product

Description	Overall general description of the container closure system, plus: For Each Packaging Component: • Name, product code, manufacturer, physical description • Materials of construction (for each: name, manufacturer, product code) • Description of any additional treatments or preparations
Suitability	Protection: (By each component and/or the container closure system, as appropriate) • Light exposure • Reactive gases (e.g., oxygen) • Moisture permeation • Solvent loss or leakage • Microbial contamination (sterility/container integrity, increased bioburden, microbial limits) • Filth • Other • Safety: (for each material of construction, as appropriate) • Chemical composition of all plastics, elastomers, adhesives, etc. • Extractables, as appropriate for the material • Extraction/toxicological evaluation studies, as appropriate • Appropriate USP testing • Appropriate reference to the indirect food additive regulations (21 CFR 174-186) • Other studies as appropriate Compatibility: (for each component and/or the packaging system, as appropriate) • Component/dosage form interaction, USP methods are typically accepted may also be addressed in post approval stability studies Performance: (for the assembled packaging system) • Functionality and/or drug delivery, as appropriate
Quality Control	For Each Packaging Component Received by the

	Applicant: • Applicant's tests and acceptance criteria • Dimensional (drawing) and performance criteria • Method to monitor consistency in composition, as appropriate For Each Packaging Component Provided by the Supplier: • Manufacturer's acceptance criteria for release, as appropriate • Brief description of the manufacturing process
Stability	• Description of packaging system used in study • Observations, results and corrective actions

Table 2: Information that typically should be submitted for solid oral drug products and powders

Description	Overall general description of container closure system, plus: For Each Packaging Component: • Name, product code, manufacturer • Materials of construction • Description of any additional treatments
Suitability	Protection: (by each component and/or the container closure system, as appropriate) • Light exposure • Moisture permeation • Seal integrity or leak tests for unit-dose packaging Safety:(for each material of construction, as appropriate) Chemical composition of all plastics, elastomers, adhesives, etc. • For tablets, capsules, and powders, appropriate reference to the indirect food additive regulation may be submitted, but may not be appropriate for powders for reconstitution • For rayon and cotton fillers, data from USP monographs. • For non-USP materials, data and acceptance criteria should be provided. • For dessicants and other absorbent materials: the size and shape should differ from the dosage form Compatibility: (on each component or the packaging system) • For glass and plastic containers, data from USP Containers testing. Performance: (on each component or the packaging system, as appropriate) • Functionality and/or drug delivery, as appropriate
Quality Control	For Each Packaging Component Received by the Applicant: • Applicant's tests and acceptance criteria • Dimensional (drawing) and performance criteria • Method to monitor consistency in composition, as appropriate For Each Packaging Component Provided by the Supplier: • Manufacturer's acceptance criteria for release, as appropriate • Description of manufacturing process, as appropriate
Stability	• Description of packaging system used in study • Observations, results and corrective actions

a) Including any additives used in the manufacture of a packaging component

b) Testing of plastics should be performed on the packaging component, not on the unformed resin.

c) Note that applicant's acceptance tests may include, among others, test parameters indicated under

d) the description, suitability, and quality control sections of this table.

Table 3: Information that typically should be submitted for liquid-based oral and topical drug products and for topical drug delivery systems

Description	Overall general description of container closure system, plus: For Each Packaging Component: • Name, product code, manufacturer, physical description. • Materials of construction (for each: name, manufacturer and product code) • Description of any additional treatments (e.g., procedure for washing) • components
Suitability	<u>Protection</u>: (by each component and/or the container closure system, as appropriate) • Light exposure • Reactive gases(e.g., oxygen) • Solvent loss • Moisture permeation (liquid-based oral products would typically meet USP • Requirements for a tight or class A container) • Microbial contamination (container integrity, increased bio burden, microbial limits, as appropriate) • Seal integrity or leak testing of tubes(topical drug products) and unit dose • Containers (liquid-based oral drug products) <u>Safety:</u> (for each material of composition, as appropriate) • Chemical composition of all plastics, elastomers, adhesives, etc. • For most liquid-based oral drug products: appropriate reference to the indirect food additive regulations • For liquid-based oral drug products with chronic dosing regimens that contain Alcohol as a co-solvent: information to establish that exposure to extractable will be no greater than that expected to result from the use of similar packaging components when used with foods or that the exposure is acceptable based on toxicological data • For topical drug products (plastic coatings for metal tubes), and plastic drug delivery system components: USP container testing. • For topical delivery systems: appropriate reference to indirect food additive regulations <u>Compatibility</u>: (for each component of the packaging system, as appropriate) • For Low Density Poly Ethylene (LDPE) and glass components, USP containers testing • For coating of metal tubes: coating integrity testing <u>Performance</u>: (for the assembled packaging system) • Functionality and/or drug delivery should be addressed, as appropriate. • For Each Packaging Component Received by the Applicant: • Applicant's tests and acceptance criteria • Dimensional (drawing) and

	performance criteria • Method to monitor consistency in composition, as appropriate
Quality Control	For Each Packaging Component Provided by the Supplier: • Manufacturer's acceptance criteria for release, as appropriate • Description of the manufacturing process, as appropriate
Stability:	• Description of packaging system used in study • Observations, results and corrective actions

Tests to be performed on Packaging System

Packaging system is the combination of container system and closure, it comprises of several layers of protection to the pharmacopoeial preparation along with some additional components like sealing devices, delivery devices, labeling and package inserts. Container material can be selected based in their properties, most of the times glass or plastic can be selected as a construction material for container closure system.

Glass Containers

Glass containers must be tested for chemical resistance and light transmission according to the described procedures in USP.

Light Transmission Test

Spectrophotometer issued for measuring the amount of light transmitted by the glass or plastic. Glass and plastic are of transparent and translucent types. The spectrophotometer with suitable sensitivity and accuracy should be chosen for measuring the amount of light transmitted. The circular piece of the material is placed in the spectrophotometer with its cylindrical axis parallel of the plane of slit and approximately centered with the slit and measure the amount of light transmitted in the region of 290 to 450 nm.

The amount of light transmitted should not exceed 10% at any wavelength for Non Parenteral (NP) glass containers and plastic containers for oral formulations. The limit for amount of light transmission has given in table 4.

Table 4: Maximum percentage of light transmission at any wavelength between 290 and 450 nm

Maximum percentage of light transmission at any wavelength between 290and450 nm		
Nominal size (mL)	**Flame sealed containers**	**Closure sealed containers**
1	50	25
2	45	20
5	40	15
10	35	13
20	30	12
50	15	10

Chemical Resistance

Chemical resistance of the container is tested for glass containers by using following tests

a. Powdered glass test

b. Water attack test

c. Arsenic

The degree of resistance is determined by amount of alkali released by attacking the container with the medium at specified conditions. The higher is the resistance the lesser will be the amount of alkali released 12-15.

In the above mentioned three tests for evaluating chemical resistance of glass, the prepared specimen of water (the specimen of water prepared by using the procedure mentioned in the USP monograph 661) should be titrated with 0.020 NH_2SO_4, methylene red issued as an indicator. The amount of acid consumed in the titration should not exceed the limits given in the table 5.

Table 5: The amount of acid consumed in chemical resistance test of glass

Type	General description1	Type of test	Limits	
			Size 2mL	mL of 0.020 N acid
I	Highly resistant, Borosilicate glass	Powdered glass test	All	1.0
II	Treated soda lime glass	Water attack test	100mL or less	0.7
			Over 100 mL	0.2
III	Sodalime glass	Powdered glass test	All	8.5
NP	General purpose sodalime	Powdered glass test	All	15
1. The description applies to containers of this type glass usually available				
2. Size indicates the over flow capacity of the glass				

Plastic Containers

The following test should be performed on the plastic containers:

1. Light transmission test (According to chapter 661of USP)

2. Water vapor permeation test (According to chapter671 of USP)

3. Physicochemical tests (According to chapter 661of USP)

- Non volatile residue
- Residue on ignition
- Heavy metals
- Buffering capacity

4. Biological tests

- *In vitro* biological tests (According chapter 87 of USP)
    - Agar diffusion test
    - Direct contact test
    - Elution test
- *In vivo biological tests (According chapter 88 of USP)*
    - Systemic injection test
    - Intra cutaneous test
    - Implantation test

Labeling

Labeling is the best source of information regarding the medication. Even though written information and oral communication with medical practitioner may be available, the label should fulfil the obligations for safe and effective use of medicine.

Product container label and carton label should communicate the critical information for safe use of medication. Some of the factors lead to medication errors, that include but not limited to are given here,

- Missing of key information like product name, strength, and dosage form
- Key information doesn't appear on the same field of vision i.e., the information is not readable without having to turn the container
- Labels which looks similar among multiple strengths of same products and similar labels among different products
- Labels which are cluttered by extraneous text or distracting images and graphics
- Error prone abbreviations or symbols
- Text is difficult to read because of typical font size, type and overlapping of the text.

Principal display panel (PDP) is the panel of label that is most likely to be displayed, presented, shown or examined by the end user. Principal display panel should contain the most prominent information like proprietary name, established name, product strength, route of administration, warnings. Other information like Rx only statement, net quantity statement, manufacturer name, and logo should not compete with important information and it is better placed on the side panel.

USFDA recommends that the text on the label should be in the same direction, same field of vision, and surrounded by adequate white space to improve the readability. The size of the label should be adequate to accommodate the important information on PDP of the label. Font size and style of the text should be easy to read and recommended size is 12-points whenever label size permits. Contrast of the text and background colour should be appropriate to afford adequate legibility of the text. Abbreviations, synonyms and acronyms which may lead to misinterpretation are not used.

Copies of Labeling to be Submitted

The archival copy of an application should contain copies of all labeling proposed for the drug product:

For draft labeling, the applicant must submit four copies. When the draft labeling is submitted, one copy should be placed in archival copy. Single copies should be placed in chemistry, pharmacology and clinical review sections of the application17.

For final printed labeling, 12 copies should be submitted. When final printed labeling and carton labeling is submitted, one copy should be mounted, bound and inserted in archival copy. The remaining 11 copies should be mounted, bounded and submitted in a separate jacket clearly labelled "**Final Printed Labeling.**"

Physician Labeling Rule (PLR)

On January 24, 2006 by making amendments to the content and format of labeling for prescription drug and biological products, FDA has designed Physician Labeling Rule to make easier for healthcare practitioner to access, read and use to make prescribing decisions. According to this rule labeling includes three sections: Highlights of prescribing information, a table of contents (contents), and the Full Prescribing Information (FPI). Highlights contain the most important and most commonly referred information from FPI. The contents include the section and subsections of the full prescribing information. Full prescribing information is the detailed description of drug for safe and effective use of the drug. Annexure II provides the prescription drug labeling for UCERIS.

PLR format contains substantially same information like old format of labeling, with some reorganizations and reordering the information16. Transition of labeling from old format to PLR format, providing an opportunity to improve the quality of labeling content and made it a better communication tool. Table 6 provides old and PLR format of labeling

Table 6: Prescription drug labeling (Old format vs. New format)

Old format	New format
Description	Highlights of prescribing information
Clinical pharmacology	Product names, Other required information
Indications and usage	Boxed warning
Contraindications	Recent major changes
Warnings	Indications and usage
Precautions	Dosage and administration
Adverse reactions	Dosage forms and strengths
Drug abuse and dependence	Contraindications
Over dosage	Warnings and precautions
Dosage and Administration	Adverse reactions
How supplied	Drug interactions Use in specific populations
Optional sections	
Animal pharmacology and/or Animal toxicology	FULL PRESCRIBING INFORMATION: CONTENTS

Clinical studies	FULL PRESCRIBING INFORMATION Boxed warning
References	• Indications and Usage • Dosage and Administration • Dosage forms and Strengths • Contraindications • Warnings and Precautions • Adverse reactions • Drug interactions • Use in specific populations • Drug abuse and Dependence • Over dosage • Description • Clinical pharmacology • Nonclinical toxicology • Clinical studies • References • How supplied/Storage and Handling • Patient counseling information

Physician Labeling Rule is being implemented on a staged implementation schedule, based on the approval date and application status, the prescription drugs which are subjected to this rule are categorized into following categories:

I. Prescription drug products for which a New Drug Application (NDA), Biologics License Application (BLA), or efficacy supplement was approved by the Food and Drug Administration (FDA) between June 30, 2001 and June 30, 2006;

II. Prescription drug products for which an NDA, BLA, or efficacy supplement is pending on June 30, 2006; or

III. Prescription drug products for which an NDA, BLA, or efficacy supplement is submitted anytime on or after June 30, 2006.

Schedule for implementing the PLR for the above categories:

1. For products for which an NDA, BLA, or efficacy supplement is submitted for approval on or after June 30, 2006, proposed conforming labeling must be submitted as part of the application.
2. For products for which an NDA, BLA, or efficacy supplement is pending on June 30, 2006, or that has been approved any time from June 30, 2005, up to and including June 30, 2006, a supplement with proposed conforming labeling must be submitted no later than June 30, 2009.
3. For products for which an NDA, BLA, or efficacy supplement has been approved anytime from June 30, 2004, up to and including June 29, 2005, a supplement with proposed conforming labeling must be submitted no later than June 30, 2010.
4. For products for which an NDA, BLA, or efficacy supplement has been approved anytime from June 30, 2003, up to and including June 29, 2004, a supplement with proposed conforming labeling must be submitted no later than June 30, 2011.
5. For products for which an NDA, BLA, or efficacy supplement has been approved anytime from June 30, 2002, up to and including June 29, 2003, a supplement with proposed conforming labeling must be submitted no later than June 30, 2012.
6. For products for which an NDA, BLA, or efficacy supplement has been approved anytime from June 30, 2001, up to and including June 29, 2002, a supplement with proposed conforming labeling must be submitted no later than June 30, 2013.

Prescription Drug Vs. Over-the-counter (OTC) Labeling

Prescription and OTC drugs must meet stringent federal regulations for safety and effectiveness. The drugs for the treatment of diseases

which can't be diagnosed by individuals, drugs which are toxic and habit forming should be used under the supervision of the physician. OTC drugs usually contain the label which gives the sufficient directions for safe use of medication. The drugs which are non-habit forming and non toxic will be dispensed under OTC category[18, 19]. Table 7 provides the labels of prescription drugs and OTC drugs.

Table 7: Prescription drug Vs. OTC drug labeling

Prescription drugs (21CFR 201.57)	**Over-the-counter products (21 CFR 201.80)**
Divided into three sections 1. Highlights 2. Contents 3. Full prescribing information **Highlights:** 1. Highlight limitation statement 2. Drug name, dosage form, route of administration and controlled substance 3. Initial US approval 4. Boxed warning 5. Recent major changes 6. Indications and usage 7. Dosage and administration 8. Dosage and form and strength 9. Contraindications 10. Warnings and precautions 11. Adverse reactions 12. Drug interactions 13. Use in specific population 14. Patient counselling information 15. Revision date **Full prescribing information contents** **Full prescribing information:** Boxed warning 1. Indications and Usage 2. Dosage and Administration 3. Dosage Forms and Strengths 4. Contraindications 5. Warnings and Precautions 6. Adverse Reactions 7. Drug Interactions 8. Use in Specific Populations 9. Drug Abuse and Dependence 10. Over dosage 11. Description 12. Clinical Pharmacology 13. Nonclinical Toxicology 14. Clinical Studies 15. References 16. How Supplied/Storage and Handling 17. Patient Counselling Information	A. Description a. Proprietary name • Type of dosage form and route of administration • Qualitative and quantitative information • Statement if sterile product • Pharmacological class • Chemical name and structural formula • If the product is radioactive information related to emission data and external radiation date included b. If appropriate others information on physicochemical properties like pH constant mentioned B. Clinical pharmacology C. Indications and usage D. Contra-indications E. Warnings F. Precautions G. Adverse reactions H. Drug abuse and dependence I. Over dosage J. Dosage and administration K. How supplied L. Animal pharmacology and animal toxicology M. Clinical studies and references

Medication Errors

Most commonly medication errors occur due to look alike or sound alike names of the medication products. Around 25% of medication errors are due to name confusion and 33% of medication errors are due to packaging and labeling confusion. Poorly worded, unclear or confusingly presented user instructions can lead

to ineffective patient compliance, adverse reactions, side-effects and at worst fatality. Withdrawal of drugs from the market and data about medication errors have demonstrated the limitations of labeling as a tool for risk management.

USFDA has taken initiatives to increase the usefulness and use of labeling by healthcare professionals and patients by change in the format and content of prescription drug labeling, implementation of bar code requirements for prescription medicines and certain OTC products and refining the evaluation procedures for proposed product names and their potential to contribute to product confusion.

Sources from labeling and packaging of product that can lead to medication errors include:

1. Lack of prominent placement of drug name and strength
2. Small size and poor readability of printed information
3. Insufficient prominence given to route of administration (e.g., Nasal vs. Injection, Intravenous vs. Intramuscular)
4. Poorly designed or cluttered labels
5. Lack of differentiation between drug products that have similar names
6. Similar-appearing labels or packages of different products
7. Poor use or absence of color to differentiate products
8. Prominence of company logos versus information that identifies the product
9. Inadequate warnings about proper drug use
10. Lack of legibility of International Non-proprietary Name (INN)s
11. Labeling cluttered with company graphics and multilingualism
12. Lack of clarity in expression of dose strengths and concentration
13. Use of similar colors for different strengths and products
14. Inaccurate dosing devices
15. Lack of safety devices
16. Uninformative package leaflets
17. The use of similar graphics for different dosage strengths intended to reinforce the brand image represents the another source of confusion

Few Recommendations to reduce the Medication Errors

1. Avoid printing of warnings on the cap or ferrule of injectables
2. Employ failure mode and effects analysis in design of devices and in the packaging and labeling of medications and related devices.
3. Bar coding system is used on the labeling of drug products
4. Print the drug name (brand and generic) and the strength on both sides of injectables and IV bags, containers, and overwraps. For large-volume parenterals, the name of the drug should be readable in both the upright and inverted positions.
5. Use the innovative labeling to aid practitioners in distinguishing between products with very similar names - for example, the use of tall letters such as Vinblastine and Vincristine.
6. Avoid printing company logos and company names that are larger than the type size of the drug name.
7. Collaboration among industry, regulators, standards-setters, healthcare professionals, healthcare organizations, and patients to facilitate design of packaging and labeling to help minimize errors.
8. Further development of the FDA's error prevention analysis efforts to provide consistent regulatory review of product labeling and packaging relative to the error-prone aspects of their design.

Special Packaging

Child Resistant Packaging

According to 16CFR1700 child resistant packaging is the packaging that designed or constructed to be difficult for children under 5years of age to open or obtain the toxic or harmful amount of the substance in the packaging within a reasonable time and not difficult for normal adults to use properly.

Child resistant packaging regulations are framed by Poison Prevention Packaging Act (PPPA) of 1970. The standards for the packaging will be based on the degree or nature of the hazard to children in the availability of such substance.

The standards of the packaging must be feasible, practicable and appropriate for such substance.

The substances which require child resistant packaging should be readily available for the elderly or handicapped persons who are unable to access the use of those substances in special packaging. For this requirement manufacturers are authorized to provide the substances in non complying packages along with complying package.

The label of the package should contain the words "This Package for Households without Young Children". This statement shall appear on the principal display panel of the immediate container as well as on the principal display panel of any outer container or wrapping used in the retail display of the substance. If a package bears more than one principal display panel, the required statement shall appear on each principal display panel of the immediate container as well as on each principal display panel of any outer container or wrapping used in the retail display of the substance.

The required labeling statement shall appear within the borderline of a square or rectangle on the principal display panel in conspicuous and easily legible capital letters, shall be in distinct contrast, by typography, layout, color, or embossing, to other matter on the package, and shall appear in lines generally parallel to the base on which the package rests as it is designed to be displayed.

The size of the declaration statement should be related to the area of principal display panel of the package and shall be uniform for all packages of substantially same size and complying with following requirements

- Not less than 1⁄16 inch in height on packages the principal display panel of which has an area of 7 square inches or less.
- Not less than 3⁄32 inch in height on packages the principal display panel of which has an area of more than 7 but not more than 15 square inches.
- Not less than 1⁄8 inch in height on packages the principal display panel of which has an area of more than 15 but not more than 25 square inches.
- Not less than 3⁄16 inch in height on packages the principal display panel of which has an area of more than 25 but not more than 100 square inches.
- Not less than 1⁄4 inch in height on packages the principal display panel of which has an area of more than 100 square inches.
- The manufacturer of substances in special packaging should submit sample of each type of special packaging, as well as the labeling for each size product that will be packaged in special packaging and the labeling for any non complying package. Sample packages should be submitted without contents when such contents are unnecessary for demonstrating the effectiveness of the packaging24.

Tamper-evident Packaging Requirements (21CFR 211.132)

- Each manufacturer and packer who packages drug product for retail sale shall package the product in a tamper-evident package.
- A tamper-evident package should have one or more indicators or barriers to entry, if the barrier is breached or missing, it should provide visible evidence to consumers that tampering has occurred.

- To reduce the chances of tampering and to facilitate consumers to discover if a product has been tampered with, the package is required to be distinctive by design or by the use of one or more indicators or barriers to entry that employ an identifying characteristics like a pattern, name, registered trademark, logo, or picture.
- The tamper evident package should be "distinctive by design" means the packaging cannot be duplicated with commonly available materials or through commonly available processes.
- A tamper-evident package may involve an immediate-container and closure system or secondary-container or carton system or any combination of systems intended to provide a visual indication of package integrity.
- The tamper-evident feature shall be designed to and shall remain intact when handled in a reasonable manner during manufacture, distribution, and retail display.
- Any two-piece, hard gelatin capsule covered by this section must be sealed using an acceptable tamper-evident technology.
- The label of tamper evident pack should bear the statement, that:
    - ✓ Identifies all tamper-evident feature(s) and any capsule sealing technologies used to comply with tamper evident requirements
    - ✓ Is prominently placed on the package; and
    - ✓ Is so placed that it will be unaffected if the tamper-evident feature of the package is breached or missing.
- If any feature is chosen as identifying characteristic to meet the tamper evident requirements, that characteristic is required to be referred to in the labeling statement. For example, the labeling statement on a bottle with a shrink band could say "For your protection, this bottle has an imprinted seal around the neck."
- A manufacturer or packer may request an exemption from the packaging and labeling requirements of this section. A request for an exemption is required to be submitted in the form of a citizen petition according to 21CFR 10.30 and should be clearly identified on the envelope as a "Request for Exemption from the Tamper-Evident Packaging Rule."

The petition is required to contain the following:

1. The name of the drug product or, if the petition seeks an exemption for a drug class, the name of the drug class, and a list of products within that class.
2. The reasons that the drug product's compliance with the tamper-evident packaging or labeling requirements of this section is unnecessary or cannot be achieved.
3. A description of alternative steps that are available, or that the petitioner has already taken, to reduce the likelihood that the product or drug class will be the subject of malicious adulteration.
4. Other information justifying an exemption25.

Packaging and Labeling Requirements for India

Container Closure System

Containers for pharmacopoeial article is intended to contain a drug substance or drug product with which it is, or may be in direct contact. The closure is a part of the container. Container should provide adequate degree of protection, minimise loss of constituents and should not interact physically or chemically with the contents in a way that will alter the quality to an extent beyond the limits given in an individual monograph, or present a risk of toxicity. The choice of container will be done based after considering all the factors like nature of articles, likely effects of transportation and storage. Materials used for containers for pharmaceuticals are majorly glass and plastic.

Glass Containers

Based on the hydrolytic resistance, glass containers are classified as:

- Type I glass containers are of neutral glass with high hydrolytic resistance, suitable for most preparations
- Type II glass containers are usually soda lime silica glass with high hydrolytic resistance. They are suitable for most acidic and neutral, aqueous preparations whether or not for parenteral use,
- Type III glass containers are soda lime silica glass with moderate hydrolytic resistance. They are generally suitable for non-aqueous preparations for parenteral use, for powders for parenteral use and for preparations not for parenteral use.

Type II and Type III glass should not be re used. Glass containers with a hydrolytic resistance higher than that recommended for a particular type of preparation may generally also be used. Containers for parenterals must be uncoloured, but for light sensitive preparations coloured glass may be used and the glass should be sufficiently transparent to permit visual inspection of the contents.

Tests to be performed on the Glass Container

The following two types of tests are done on the containers to define the type of container

- ✓ Test 1 is to distinguish type I and II glass from type III glass
- ✓ Test 2 is done to know whether the high hydrolytic resistance is due to the chemical composition or due to surface treatment and to distinguish type I and type II glasses
- ✓ Test for Arsenic.

Test 1

Carry out the determination on the unused containers. The number of containers to be examined and the volumes of test solution to be used are given in Table 8.

Prepare the test solution according to the procedure mentioned in Indian Pharmacopoeia and titrate the solution with 0.01M Hydrochloric acid using 0.15ml of methyl red solution per each 50ml of test solution as an indicator. Calculate the volume of 0.01M Hydrochloric acid per 100mL of test solution. The amount of acid should not be greater than the volume mentioned in the following table 9.

Table 8: Number containers to be used and the volume of test solution to be used in test 1

Nominal capacity of container (ml)	Number of containers to be used	Volume of test solution to be Used for titration (ml)
Up to 3	At least 20	25.0
5 or less	At least 10	50.0
6 to 30	At least 5	50.0
More than 30	At least 3	100.0

Table 9: Limits for the amount of acid consumed in the test 1

Capacity of container [corresponding to 90 per cent average overflow volume (ml)]	Volume of 0.01M hydrochloric acid per 100 ml of test solution	
	Type I or II glass (ml)	Type III glass (ml)
Not more than 1	2.0	20.0
More than 1 but not more than 2	1.8	17.6
More than 2 but not more than 5	1.3	13.2
More than 5 but not more than 10	1.0	10.2
More than 10 but not more than 20	0.80	8.1
More than 20 but not more	0.60	6.1
More than 50 but not more than 100	0.50	4.8
More than 100 but not more than 200	0.40	3.8
More than 200 but not more than 500	0.30	2.9
More than 500	0.20	2.2

Test 2

This test can be used to distinguish Type I and Type II glass containers. Fill the containers with

4% (v/v) Hydrofluoric acid and allow it to stand for 10minutes at room temperature and empty the containers. Then follow the same procedure which is used in Test 1.

- For Type I glass the values obtained with the hydrofluoric acid-treated containers are closely similar to those stated in the Table for Type I or Type II glass.
- For Type II glass the values obtained with the hydrofluoric acid-treated containers greatly exceed those given in the Table for Type I or Type II glass and are similar to those given
- For Type III glass.

Test for Arsenic

Prepare the test solution according to the procedure given in Indian Pharmacopoeia. Compare the absorbance of the test solution with standard arsenic solution (10ppm) at a wavelength of 847nm. The absorbance of test solution should not exceed the absorbance of standard arsenic solution. Hydrazine molybdate reagent is used as a solvent and blank for the determination of absorbance.

Plastic Containers and Closures

Plastic containers used for pharmaceuticals are prepared from different types of polymers like, polyethylene (low or high density), poly propylene, Poly Vinyl Chloride (PVC), polystyrene and very few times with poly ethylene terephthalate (PET). The type of plastic container can be selected after assessing the possible hazard to the product from the container material by using the data from the supplier of the raw material and composition of the container material.

The type containers selected should be such that the ingredients of the product in contact are not significantly absorbed or not significantly migrate into the plastic.

Containers should be manufactured from materials that do not include any substances in their composition which can be extracted by any contents in such quantities to alter the efficacy or stability of the product or to present a toxic hazard.

The product which is packed in the container should be examined to ensure the absence of any sensory, chemical or physical change. The container closure system must be assessed for change in the quantity of the contents due to permeability of the plastic, any change in the pH, assessment for effects of light, chemical tests, and biological tests (if necessary) are done.

Tests for Plastic Container

1. Leakage test / Collapsibility test
2. Acidity or Alkalinity
3. Light absorption
4. Reducing substances
5. Transparency
6. Labeling

Tests for Container Material

These tests are to be done on the portions of container that are unlabelled, un-laminated.

1. Test for Barium
2. Test for Heavy metals
3. Test for Zinc
4. Test for Tin
5. Residue on ignition
6. Biological tests
    a. Systemic injection test
    b. Intracutaneous test

Closures for Containers of Parenteral Products

Closure of the container is a packaging component which is in direct contact with the drug. The closures chosen for use with a particular preparation should be such that the components of the preparation in contact with the closure are not adsorbed onto the surface of the closure to an extent sufficient to affect the product adversely. The closure should not yield to the product substances in quantities sufficient to affect its stability or to present a risk of toxicity. The closures should be compatible with

the preparation for which they are used throughout the shelf-life of the product.

The closures chosen for use with a particular preparation should be such that the components of the preparation in contact with the closure are not adsorbed onto the surface of the closure to an extent sufficient to affect the product adversely. The closure should not yield to the product substances in quantities sufficient to affect its stability or to present a risk of toxicity. The closures should be compatible with the preparation for which they are used throughout the shelf-life of the product[21, 22].

The following tests are to be done on the closure

1. Appearance of the solution
2. pH of aqueous extract
3. Light absorption
4. Reducing substances
5. Heavy metals
6. Residue on evaporation
7. Volatile sulphides
8. Sterilization tests
9. Fragmentation tests
10. Self-sealability
11. Biological tests

Child Resistant Packaging Regulations in India

Indian Standard Child Resistant Packaging – Requirements and testing procedures for reckonable packages provides the guidance for CR packaging in India, this Indian standard has adopted by Bureau of Indian Standards on the recommendation of the Packaging Codes Sectional Committee and approval of the Light Mechanical Engineering Division Council.

This guidance provides the requirements and test procedures for reckonable packages. This guidance is intended for type approval only, not for quality assurance purpose. Table 10 provides the comparison of child resistant packaging regulations in India and USA.

Definitions

Child Resistant Package

A package which is difficult for young children under the age of five to open [or gain access to the contents], but which is not difficult for adults to use properly in accordance with the requirements of this international standard.

Reckonable Package

Any package which, after it has been initially opened, is capable of being reclosed with a similar degree of security and capable of being used a sufficient number of times to dispense the total contents without loss of security.

Test Requirements and Procedures

Sufficient number of packages shall be submitted to enable a representative sample to be selected for testing and to provide a reserve for reference purpose. The manufacturers should satisfy themselves that the life expectancy of the package will exceed the maximum expected number of openings and closings which are likely to occur in practice. Testing should be carried out in two classes of people i.e., young children of 42 to 51 months age and adults between 18 to 65 years age. At least 85% of children in the test group shall not be able to open the package within 5min. At least 80% children shall not be open the package within 5 min, without demonstration and remaining 5% children has given a demonstration and allowed to open in next 5min. In case of adults at least 90% of adults shall be able to open the package within 5min, without demonstration. The tests should be conducted under the supervision of qualified person. If the test package contains any hazardous substance, it has to be replaced with inert substitute material before the test has begun. The substitute material is filled up to nominal capacity of the package.

Child Test

A group of 200 children of age 42 to 51 months with an even distribution of age and sex has to be used. The groups should represent social, ethnic and cultural origins of the country as a whole. Healthy and with no physical and mental

handicap subjects shall are included in the test group. The subject should not be the person who has already participated in earlier test, if the subject has already participated the earliest package must be with different mechanism of packing or there should be at least one week difference between two tests. The location of the test should be familiar to the children. Procedure and instructions are explained in the guidance. The results should be recorded clearly that whether the successful opening of package by children is with demonstration or without demonstration and usage of teeth also should be mentioned.

Adult Test

A group of 100 subjects are selected as test group, which includes 70% of female subjects. 80% of the subjects should be of age between 18 to 60 years and remaining 20% are of the age between 61 to 65 years. Each adult should be given a package along with the accessories and printed instruction to open and reclose the package properly. Demonstration is not given. The results should be recorded whether the adult is successful in opening and reclosing the package within 5 min.

Assessment of Results

In case of child test the result is failure if the subject is able to open the package within min. In case of adult test the result is failure if the subject is not able to open and reclose it properly within 5 min.

Test Report

The following information should be included in test report of child and adult test;

The name of agency carrying out the test

The date on which the test is carried out

The name and address of the manufacture or supplier

The name of the person supervising the test

Complete description of the package tested

The copy of the instructions given to the adult subject description of the substitute product if it is used in the test

Child Test

The following information is specific for child test;

- Location of the test
- The number, name, age and sex of the children involved
- The number of children (age and sex) who successfully opened the package [before demonstration, after demonstration, the means used for successful opening of the package]
- The percentage of children failed to open the package (if the full test is performed)

Adult Test

The following information shall be recorded

- The number, age and sex of the adults involved
- The number, age and sex of the adults who has successfully open and reclosed the package properly
- The number of subjects, who opened, but couldn't close the package properly
- The number of subjects who has failed to open the package
- The percentage of adults who opened and reclosed the package properly (if the full test has been carried out)

The overall report of the test is whether the test is Pass or Fail.

The additional information like, the time required for the adult and children to open the package is included, if necessary[23].

Labeling Requirements in India

Labeling is any printed or written information accompanied by the medicinal product, which provides the comprehensive and concise statement of a drug's quality, safety and efficacy. It includes the information regarding the indications, effects, dosage form, frequency and duration of administration, precautions and other

Table 10: Comparison of Child Resistant (CR) packaging requirements of India and USA

S. No	Requirements	India	USA
1	Guidance	Child resistant packaging- requirements and testing procedures for reclosable packages	16CFR 1700 Poison prevention Packaging
2	Source authority of guidance	ISO 1387: 1989	Consumer Product Safety Commission
3	Definitions	Not clear	Clearly defined
4	Standards for special packaging	No standard requirements are established	Standard requirements are established (§1700.3)
5	Non complying packaging requirements	Not explained	Explained (§1700.5)
6	Substances required for CR packaging	Not mentioned	Clearly mentioned (§1700.14)
7	Submission of sample packages to authority	Not mentioned clearly. Sufficient number of samples are provided to enable representative sample to be selected	Clearly mentioned (§1700.14)
8	Use of substitute product in tests	Substitute product is used in case of harmful products	Actual product is used
9	Storage of the pack at test location	Not mentioned	Clearly mentioned
10	Composition of test group	Vague	Clear description is given
11	Outer package	Not explained	Clearly explained
12	Calculation of age	Not explained	Clearly explained
13	Consent from the patient / subject	Not described	Described and format of consent form is provided
14	Demonstration	Not explained	Clearly explained
15	Instruction to be given to the participants in tests	Not explained	Clearly explained
16	Elimination of the participants	Not discussed	Discussed about the elimination of the subjects
17	Report	Includes the name of agency, manufacturer, supervisor etc.	Not given

related information. The safe use of medicines depends on the information presented on the label and package. All labels must be clear and concise and must bear all the information for safe use of medicine.

Regulatory Requirements for Labeling

Manner of labeling (Rule 96 of D & C act rules) states the minimum requirements to be presented in the labeling. If any drug product is not labeled in the prescribed manner or if its label or container or anything accompanying the drug bears any statement, design or device which makes any false claim for the drug or which is false or misleading will be considered as misbranded drug.

The following information should be printed or written in indelible ink and shall appear in a conspicuous manner on the label of the inner most container of any drug on every other covering in which the container is packed.

1. The name of the drug The proper name of the drug shall be printed or written in a more conspicuous manner than the trade name, if any, which shall be shown immediately after or under the proper name
2. A correct statement of the net content in terms of weight, measure, volume, number of units of contents, number of units of activity, as the case may be, and the weight, measure and volume shall be expressed in the metric system.
3. The content of active ingredients.
    - For liquid orals the content of active ingredient expressed as an amount per single dose where the dose is more than 5mL, if the dose is lesser than 5mL, the content expressed per 1 mL.
    - For liquid parenteral preparations ready for administration in terms of 1 mL or percentage by volume or per dose in the case of single dose container.
    - For drugs in solid form which are intended for parenteral administration, in terms of units or weight per milligram or gram.
    - For tablets, capsules, pills and the like, in terms of the content in each tablet, capsule, pill or other unit
    - For other preparations, in terms of percentage by weight or volume or in terms of unit per gram or mL Content of the active ingredient is not required to include on the label in of pharmacopoeial preparation where the composition of such preparation is specified in the respective pharmacopoeia and to a preparation included in the National Formulary of India (NF)
4. The name of the manufacturer and the address of the premises of the manufacturer where the drug has been manufactured. If the container is smaller to accommodate all the details, the name and principal place of manufacture is enough to show on the container
5. A distinctive batch number. The representation of batch number is preceded by the words, Batch No. or B. No. or Batch or Lot No. or Lot.
6. Every drug manufactured in India shall bear on its label the number of the licence under which the drug is manufactured, the figure representing the manufacturing licence number being preceded by the words “Manufacturing Licence Number” or “Mfg. Lic. No.” or “M.L.”
7. Drugs mentioned in Schedule P or combination of drugs which have schedule P drugs with it, shall bear the date of manufacture, date of expiry of potency, the period between date of manufacture and date of expiry should not exceed the period mentioned in the schedule for schedule P drugs, for drugs other than schedule P drugs the label should bear the date of manufacture and date of expiry and the date of expiry should not be later than 6months from date of manufacture. the date of expiry shall be in terms of month and year and it shall mean that the drug is recommended till the last day

of the month. The date of expiry shall be preceded by the words 'Expiry date'

8. If the drugs are imported, the label shall bear the number of license under which it is imported, and preceded by the words 'Import License'.
9. Every drug intended for distribution to the medical profession as a free sample, shall, bear on the label of the container the words 'Physician's Sample—Not to be sold' which shall be overprinted.
10. If any preparation contains not less than 3 per cent by volume of alcohol the quantity of alcohol shall be stated in terms of the average percentage by volume of absolute alcohol in the finished products.
11. The label of innermost container of the following categories of drugs and every other covering in which the container is packed shall bear a conspicuous red vertical line on the left side running throughout the body of the label which should not be less than
12. 1mm in width and without disturbing the other conditions printed on the label.
13. Narcotic analgesics, hypnotics, sedatives, tranquilizers, corticosteroids, hormones, hypoglycemic, antimicrobials, antiepileptics, antidepressants, anticoagulants, anticancer drugs and all other drugs falling under Schedules 'G', 'H', and 'X'
14. This requirement is not applicable for ophthalmic products, ear drops, sterile preparations, and preparations for external use and animal use.
15. The above mentioned information should be printed or written in indelible ink either on the label borne by the container, or on the label or wrapper affixed to any package in which the container is issued for sale.
16. The particulars on the label can be etched, painted or otherwise indelibly marked on the container instead of being displayed on the label.
17. According the Rule 97 of the D & C act the label should contain the following cautionary statements.
    a) If the container contains the product specified in schedule G, the label should bear the word '**Caution: It is dangerous to take this preparation except under medical supervision**' conspicuously printed and surrounded by a line within which there shall be no other words.
    b) If it contains a substance specified in Schedule H be labelled with the symbol **Rx** and conspicuously displayed on the left top corner of the label and be also labelled with the following words: "**Schedule H drug - Warning : To be sold by retail on the prescription of a Registered Medical Practitioner only**."
    c) If it contains a substance specified in Schedule X, be labelled with the symbol **XRx** which shall be in **RED** conspicuously displayed on the left top corner of the label and be also labelled with the words: **Schedule X drug " Warning: To be sold by retail on the prescription of a Registered Medical Practitioner only**."
    d) If narcotic drugs and schedule H drugs are packaged in the container, the label should bear a symbol **NRx** which shall be in **RED** conspicuously displayed on the left top corner of the label and be also labelled with the words: **Schedule X drug " Warning: To be sold by retail on the prescription of a Registered Medical Practitioner only**."
18. The containers for ointments, lotions, etc. should contain the statement in capital letters "FOR EXTERNAL USE ONLY". Annexure I provides various labels with specific statements.

Package Inserts

Package inserts includes adequate directions for use. It is helpful for the physician in making correct decision before prescribing any drug for a

particular patient. Package inserts should be written in English.

Package insert is divided into two parts:

1. Therapeutic indications
    a) Posology and method of administration
    b) Contraindications.
    c) Special warnings and special precautions for use, if any.
    d) Interaction with other medicaments and other forms of interaction. e. Pregnancy and lactation, if contra-indicated.
    e) Effects on ability to drive and use machines, if contra-indicated. g. Undesirable effects/side effects.
    f) Antidote for overdosing
2. Pharmaceutical information
    a) List of excipients
    b) Incompatibilities
    c) Shelf life in the medical product as packaged for sale.
    d) Shelf life after dilution or reconstitution according to direction.
    e) Shelf life after first opening the container.
    f) Special precautions for storage.
    g) Nature and specification of the container.
    h) Instructions for use/handling

Table 10 provides the summary chart for packaging and labeling of India and USA

Labeling Requirements for ANDA Submission

A generic drug product can prove to be comparable to the innovator product in dosage form, strength, route of administration, quality, performance characteristics and intended use via an Abbreviated New Drug Application.

According to Hatch-Waxman act, if the generic product is proved bioequivalent to the innovator drug, the generic can claim the exact labeling content as the innovator. An ANDA applicant must submit draft of all the labeling components of the proposed generic product and the label must match the label of Reference Listed Drug (RLD).

Labeling information will be included in Module 1, section 1.14.1 and 1.14.3 of an eCTD application.

The draft labeling also submitted as separate Compact Disk (CD) for ANDAs in traditional format. The generic labeling must be based in the most recent version of RLD labeling.

The labeling submission includes:

1) The RLD's labeling,
2) The generic product's draft label (proposed labeling),
3) A statement that the proposed labeling is the same as RLD's labeling except for some allowed differences described in 21 CFR 314.94 (8) (iv)
4) The labeling history documents
5) A comparison of the approved (RLD) label versus the proposed label

The comparison of RLD labeling and proposed labeling must be submitted in side-by-side comparison (Table 12) to demonstrate that the labeling components of the proposed generic drug product are the same as the label approved for the RLD. Aside from the allowable changes, all other components of the proposed label represent an exact "cut and paste.

The applicant is allowed to submit the differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines without the petition according to 21CFR314.93, but for some differences like change in route of administration, dosage form, and strength in which the active ingredient is substituted for one of the active ingredients in a listed combination drug, the applicant has to get the permission before submitting the abbreviated application.

Section 1.14.1 and 1.14.3 of Module 1 of CTD provides the labeling information for an ANDA application (Table 12).

Table 11: Summary chart for Packaging and Labeling requirements for India and USA

Packaging and Labeling requirements for India and USA		
Requirement	**India**	**USA**
Packaging information to be included in the application	A brief discussion on the container closure system, name and address of the manufacturer of container closure system, this includes the tests performed on the packaging system, stability study report in the proposed container, dimensional description of the container closure system	A brief discussion on container closure system like product name, physical description of container closure system and all the components, name and address of the manufacturer of container, detailing of MOC, description about the operations carried out on the packaging system, chemical composition of each material, results of the tests to evaluate the container closure system, report of stability study on the proposed packaging system should be provided
Container closure section in the application	For drug substance 3.2.S.6 of Module 3 For drug product 3.2.P.7 of Module 3	For drug substance 3.2.S.6 of Module 3 For drug product 3.2.P.7 of Module 3
Tests to be performed on the container closure system	For glass containers Test 1, Test 2 and Test for Arsenic has to be performed For plastic containers leakage test, acidity test, light absorption test, reducing substances, transparency tests The tests should be performed according to IP procedures	For glass containers light absorption test, chemical resistance test For plastic containers light transmission test, water vapour permeation test, physicochemical test, biological test should be performed The tests should be performed according to USP
Number of copies of labeling	–	For draft labeling 4 copies and For final labeling 12 copies of the label should be submitted
Format of labeling submission	SPC format	PLR format
Labeling requirements for Primary Label		
Product description	**India**	**USA**
Trade name	Yes	Yes
Generic name	Yes	Yes
Strength	Yes	Yes
Dosage form	Yes	Yes
Amount volume/ Number	Yes	Yes

Tracing		
Manufacturing date	Yes	Not mandatory
Manufacturer name and address	Yes	Yes
NDC number	Not mandatory	Yes
Manufacturing license number	Yes	Not mandatory
Batch No.	Yes	Yes
Expiry date	Yes	Yes
Bar code	Yes	Yes
Usage and Storage information		
General indications for use	Yes	Yes
General dosage instructions	Yes	Yes
Storage instructions	Yes	Not mandatory
Miscellaneous		
Price	Yes	Not mandatory
Precautions and warnings	Yes	Not mandatory

Table 12: Labeling check list for ANDA submission (Module 1)

1.14.1	Draft Labeling (Multi Copies N/A for E-Submissions) 1.14.1.1 Four copies of draft for paper submission or 1 copy for electronic (each strength and container) 1.14.1.2 Side by side labeling comparison of container(s) and carton(s) for each strength with all differences visually highlighted and annotated, 1.14.1.3 One package insert (content of labeling) in PDF and WORD format, and Structured Product Labeling (SPL) submitted electronically. 1.14.1.4 Labeling Comprehension Studies
1.14.3	Reference Listed Drug Labeling 1.14.3.1 One side by side labeling (package and patient insert) comparison with all differences visually highlighted and annotated. 1.14.3.3 RLD package insert, 1 RLD container label, and if applicable, 1 RLD outer carton label, for each strength.

Labeling of ANDA must be updated according to the RLD labeling and it should be submitted as a special supplement- Changes being affected26, 27. This supplement should include

- 12 copies of final printed labeling The date the revised labeling will come into effect
- A side-by-side comparison of the ANDA labeling with the approved labeling of the RLD with all differences annotated and explained.

CONCLUSION

This project work provides an overview of regulatory requirements and tests for Quality control and suitability of packaging and labeling of prescription and Over-The-Counter (OTC) Products in USA and India.

As packaging protects the product form the time of manufacturing till to reach the consumer and complete usage of the product for treatment, the regulatory agencies have given sufficient instructions to the manufacturers of the pharmaceuticals with the aim of safety of the product as well as the patient.

The study had been informative to understand the need and importance of the labeling requirements of pharmaceuticals to protect the consumers by providing the suitable instructions for the use of the drug product at suitable place and suitable format.

Guidance provides the recommendations for submission. Manufacturer should ensure that the requirements are fulfilled to establish, that the quality of the product is not affected by the packaging material; the label provides the clear identification of the product and gives unambiguous directions to the consumer for the safe use of medicine.

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