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A Comparative Study of Packaging, Labelling and Container Closure Systems of Various Regulatory Bodies

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ABSTRACT

Regulatory affairs professionals are key players in drug development for obtaining approvals and maintaining life cycle management of both branded and generic drugs. Packaging has been around for many hundreds of years in some shape or form, from the early days of using wooden barrels to transport water to today's rather sophisticated methods. For identification purposes packaging must be labelled in some way and the traditional methods for doing so would be to print and apply a label to the product. Packaging also plays an important role for portraying information about the product. Outside packaging may contain directions on how to use the product or make the product. Packaging can also differentiate one brand of product from another brand. Regulatory issues around packaging are very complex, and you must consider them in detail with respect to each product's unique needs and the properties of its potential package. The role of packaging and labeling in society is a vitally important one, not only in ensuring the safe delivery of products to the end-user but also in communicating the nature of the product and how it should best be utilized. With the increased importance placed on self-service marketing, the role of packaging and labeling is becoming quite significant.

Keywords: Regulatory affairs, Packaging, Generic drugs, Brand, Product

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1. Introduction

Regulatory Affairs:

Regulatory Affairs in the pharma industry may be defined as "The interface between the pharmaceutical company and the regulatory agencies across the world." Regulatory agency may be defined as "The competent government agency which is responsible for ensuring that medicines work and are acceptably safe."

Packaging:

Packaging is defined as a technique which allows containment of pharmaceutical product from the time of production in a unit till its use. Packaging is a key for sale,

safety and success. Pharmaceutical packaging has to be carried out for the purpose of the safety of the pharmaceutical preparations in order to keep them free from contamination, hinder microbial growth, and ensure product safety through the intended shelf life for the pharmaceuticals. Packaging is a critical tool in the pharmaceutical industry for product delivery and regulatory compliance.

Functions of Packaging

Containment: The containment of the product is the most fundamental function of packaging for medicinal products. To be strong enough to hold the contents when subjected to normal handling.Not to be altered by the ingredients of the formulation in its final dosage form.

Protection: The packaging must protect the product against-Light,Moisture,Oxygen.,Biological contamination and Mechanical damage.

Stability: It is necessary to know the possible interactions between the container and the contents. Normally, product/ component stability and compatibility are confirmed during the primary research and development stage

Storage: Packaging materials should be stored in accordance with GMP for storage areas-

- Store under normal storage conditions
- Store between 2 and 8 °C (under refrigeration, no freezing)
- Store below 8 °C (under refrigeration)
- Store between -5 and -20 °C (in a freezer)
- Store below -18 °C (in a deep freezer)

Types of Packaging

Immediate (Primary) Pack: Contains and protects the dosage form so is normally in contact with it. It bears appropriate label(s) providing content and usage information. Immediate pack components are considered essential to the stability of their contents, whether or not in contact with them.

Secondary Pack: A pack component with no product contact but may add protection to that provided by the immediate pack.

Container Closure System: The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection (e.g. light barrier) of the drug product.

Marketing Pack: Combination of primary and secondary packaging, labelling, associated components (e.g., dosing cups, droppers, spoons), and external packaging (e.g., cartons or shrink wrap).

Types of Packaging Materials:

The most commonly used packaging materials and containers are:

Table 1: Table showing Types of Packaging Materials

Types of Materials	Uses
Cardboard	Boxes, Display units
Paper	Labels, Leaflets
Glass	Ampoules, Bottles, Vials, Syringes, Cartridges
Plastic	Closures, Bottles, Bags, Tubes, Laminates with paper or foil
Metal e.g. aluminium	Collapsible tubes, Rigid cans, Foils, Needles, Gas cylinders, Pressurized containers
Rubber	Closures, including plungers

Evaluation Tests:

The following are the evaluation tests for different types of packaging material:

Evaluation Test for Glass Containers:

- Crushed – glass test
- Whole-Container test
- Water Attack Test
- Powdered Glass Test

Evaluation Test for Plastic Containers:

- Leakage test
- Collapsibility Test
- Clarity of aqueous extract
- Transparency test
- Water vapour permeability test

Evaluation Test for Closures:

- Penetrability
- Fragmentation test
- Self sealability test
- Extractive test
- Compatibility test
- Light absorption test

Labelling:

The term "labelling" 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 term "label" means a display of written, printed, or graphic matter upon the immediate container of any article. Labelling covers both outer packaging and inner packaging. Labelling ensures that the critical information necessary for the safe. The particulars appearing on the label of all medicinal products should be printed in characters of at least 7 points leaving a space between lines of at least 3 mm.

Importance:

The purpose of a medicine label is to provide information about the product such as its

- Identity
- Potency
- Content
- Storage
- Expiry date
- Registration status and
- Sponsor

Label Requirements:

Containers, and the primary packs (if any) in which therapeutic goods are packed, must each bear a label or labels which comply with the following requirements:

- The particulars required by this Order to be included on a label or labels must be clearly visible and must be written**.**
- The name of the FPP.
- Method of administration.
- A list of API(s) showing the amount of each present in a dosage unit, and a statement of the container, e.g. number of dosage units, weight or volume.
- List of excipients known to be a safety concern for some patients, e.g. lactose, gluten, metabisulphite, parabens, ethanol, or tartrazine.
- Instruction on use.
- The batch number assigned by the manufacturer.
- The expiry date in an uncoded form.
- Storage conditions or handling precautions that may be necessary.
- Directions for use, and any warnings or precautions that may be necessary.
- The name and address of the manufacturer, company or person responsible for placing the product on the market.

Types of Labels: Paper is most commonly used for labels

- Plain paper label
- Gummed paper label
- Self-adhesive label
- Heat sensitive label
- In- mold label
- Shrink sleeves

2. Various Regulatory Bodies

Food and Drug Administration (FDA):

The U.S. Food and Drug Administration (FDA) is the agency within the U.S. Department of Health and Human Services (HHS) responsible for ensuring the safety and effectiveness of products. These include human and animal drugs, food supply, biological products, medical devices, cosmetics, radiation-emitting products, and tobacco products. FDA is facing a critical set of public health challenges. FDA's primary responsibility is to protect the American people from unsafe or mislabelled food, drugs, and other medical products. The FDA also guides and oversees the development and availability of effective new medical products and new food products that harness the latest advances in science and technology to improve the health and well-being of American consumers.

Therapeutic Goods Administration (TGA):

The main headquarters of TGA is located in Narrabundah Lane, Australia. The Therapeutic Goods Administration was established in 1990 to "safeguard and enhance the health of the Australian community through effective and timely regulation of therapeutic goods". It provides a national system of controls relating to the quality, safety, efficacy and timely availability of therapeutic goods used in, or exported from, Australia .The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices. The TGA administers the Therapeutic Goods Act 1989 (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary. The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices. The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.

Medicines and Healthcare Products Regulatory Agency(MHRA):

The Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (UK) is the regulatory authority (collectively, the regulatory authorities) with responsibility in their respective countries for the authorisation, granting, renewal, variation, suspension, and revocation of licences, certificates, or other regulatory mechanisms relating to those medicinal products and medical devices for human use which are clinically investigated, marketed, supplied, manufactured, or assembled in the UK . The Medicines and Healthcare Products Regulatory Agency was formed in 2003 with the merger of the Medicines Control Agency (MCA) and the Medical Devices Agency (MDA). In April 2013, it merged with the National Institute for Biological Standards and Control (NIBSC) and was rebranded, with the MHRA identity being used solely for the regulatory the centre within the group.

World Health Organisation (WHO):

The World Health Organization is a specialized agency of the United Nations (UN) that is concerned with international public. It was established on 7 April 1948, headquartered in Geneva, Switzerland. The WHO is a member of the United Nations Development Group. The WHO is responsible for the World Health Report, a leading international publication on health, the worldwide World Health Survey.

Qualification and Quality Control of Packaging Components

CDER and CBER approve a container closure system to be used in the packaging of a human drug or biologic as part of the application (NDA, ANDA) for the drug or biologic. A packaging system found acceptable for one drug product is not automatically assumed to be appropriate for another. Each application should contain enough information to show that each proposed container closure system and its components are suitable for its intended use. The type and extent of information that should be provided in an application will depend on the dosage form and the route of administration.

Injectable Drug Products

Injectable drug products may be liquids in the form of solutions, emulsions, suspensions, or dry solids that are to be combined with an appropriate vehicle to yield a solution or suspension. Injections are classified as small-volume parenterals (SVPs), if they have a solution volume of 100 ml or less, or as large-volume parenterals (LVPs), if the solution volume exceeds 100 mL. Cartridges, syringes,

vials, and ampoules are usually composed of Type I or II glass, or polypropylene. Flexible bags are typically constructed with multilayered plastic. Stoppers and septa in cartridges, syringes, and vials are typically composed of elastomeric materials. Hemolytic effects may result from a decrease in tonicity and pyrogenic effects may result from the presence of impurities. A disposable syringe may be made of plastic, glass, rubber, and metal components, and such multicomponent construction provides a potential for interaction that is greater than when a container consists of a single material. Injectable drug products require protection from microbial contamination (loss of sterility or added bioburden) and may also need to be protected from light or exposure to gases (e.g., oxygen). Liquid-based injectables may need to be protected from solvent loss, while sterile powders or powders for injection may need to be protected from exposure to water vapor. For elastomeric components, data showing that a component meets the requirements of USP Elastomeric Closures for Injections will typically be considered sufficient evidence of safety. For plastic components, data from USP Biological Reactivity Tests will typically be considered sufficient evidence of safety Extractables should be identified whenever possible. For a glass packaging component, data from USP Containers: Chemical Resistance — Glass Containers will typically be considered sufficient evidence of safety and compatibility.

Ophthalmic Drug Products:

These drug products are usually solutions marketed in a LDPE bottle with a dropper built into the neck (sometimes referred to as *droptainer*), or ointments marketed in a metal tube with an ophthalmic tip (see section III.F.2 for a more detailed discussion of tubes. The American Academy of Ophthalmology (AAO) recommended to the Agency that a uniform color coding system be established for the caps and labels of all topical ocular medications. An applicant should either follow this system or provide an adequate justification for any deviations from the system. The AAO color codes, as revised and approved by the AAO Board of Trustees in June 1996. Although ophthalmic drug products can be considered topical products (section III.F.2), they have been grouped here with injectables because they are required to be sterile (21 CFR 200.50(a)(2)and the descriptive, suitability, and quality control information is typically the same as that for an injectable drug product.

Post approval Packaging Changes:

For an approved application (NDA, ANDA or BLA), a change to a container closure system, to a component of the container closure system, to a material of construction for a component, or to a process involving one of the above must be reported to the application. The filing requirements are specified under 21 CFR 314.70 (supplements and other changes to an approved application) for an NDA or ANDA, and under 21 CFR 601.12 (changes to an approved application) for a BLA. The submission should address the items described and discussed in sections III.B and III.C of this guidance. The Agency intends to provide additional guidance on post approval changes in container closure systems in the future.

3. Regulatory Requirements

Table 2: Table showing The Federal Food, Drug, and Cosmetic Act

Sections	Title
Section 501	Adulterated drugs and devices
Section 502	Misbranded drugs and devices
Section 505 Section 505(b)(1)(D)	Description of the drug approval process. A full description of the methods used in, and the A-2facilities and controls used for, the manufacture, processing, and packing of such drug.

Table 3: Table showing the Code of Federal Regulations

Section	Title
21 CFR 211 Subpart E Subpart F Subpart G	Current Good Manufacturing Practice for Finished Pharmaceuticals Control of Components and Drug Product Containers and Closures (21 CFR 211.80 - 211.94). Production and Process Controls (21 CFR 211.100 - 211.115). Packaging and Labeling Control (21 CFR 211.122 - 211.137)
16 CFR 1700-1702	Special Packaging
21 CFR 174-186 i. Part 174 ii. Part 175 iii. Part 176	Indirect Food Additive Regulations Indirect Food Additives: General Indirect Food Additives: Adhesives and Components of Coatings e.g., 175.105 Adhesives 175.300 Resinous and polymeric coatings. Indirect Food Additives: Paper and Paperboard

iv. Part 177	Components e.g., 176.170 Components of paper and paperboard in contact with aqueous and fatty foods 176.180 Components of paper and paperboard in contact with dry food.
v. Part 178	Indirect Food Additives: Polymers e.g., 177.1380 Fluorocarbon resins 177.1520 Olefin polymers 177.1630 Polyethylene phthalate polymers.
vi. Part 180	Indirect Food Additives: Adjuvants, Production Aids, and Sanitizers. Food Additives Permitted in Food or in Contact with Food on an Interim Basis Pending Additional Studies e.g., 180.22 Acrylonitrile copolymers.
vii. Part 182	Substances Generally Recognized as Safe e.g., 182.70 Substances migrating from cotton and cotton fabrics A-5 used in dry food packaging 182.90 Substances migrating to food from paper and paperboard products.
viii. Part 186	Indirect Food Substances Affirmed as Generally Recognized as Safe (GRAS) e.g., 186.1673 Pulp.
21 CFR 600, Subpart B i. 21 CFR 600.11(h) ii. ii. 21 CFR 601.2	Biologics Provisions, Establishment Standards Containers and Closures. Applications for Licenses; Procedures for Filing.
21 CFR 201	Labeling
21 CFR 310.509	Parenteral drug products in plastic containers.
21 CFR 200.50(a)(3)	Containers of ophthalmic preparations.

Table 4: Table Showing MHRA Recommendations for the Labelling

Contents	**Requirements**
General Considerations	Labelling ensures that the critical information necessary for the safe use of the medicine islegible, easily accessible and that users of medicines are assisted in assimilating thisinformation so that confusion and error are minimize.
Name of The Medicine	The full name of the medicinal product, with its strength and its pharmaceutical form, and, if appropriate, whether it is intended for babies, children or adults, should appear on the outer packaging and on the immediate packaging to aid accurate identification of the medicinal product.
Strength and Total Content	Different strengths of the same medicinal product should be expressed in the same manner .Trailing zeros should not appear The use of decimal points should be avoided where these can be removed.
Route of Administration	The summary of product characteristics (SPC) should only according to the standard terms. Negative statements should not be used. Other nonstandardroutes of administration should be spelled out in full. Some routes ofadministration will be unfamiliar to patients and may need to be explained within thepackage leaflet. This is particularly important when medicinal products are made availablefor self-medication.
Design And Layout	Use of a large type size will be appropriate, although other factors may also be importantin making the information legible. The number of colours used on packs will needcareful consideration as too many colours could confuse.
Templates for Labelling	The templates provided in all EEA languages on the EMEA reflect the particulars whichmust appear on the labelling and package leaflet of medicinal products according toDirective 2001/83/EC.
Other Information	The “blue box” requirements in the centralized procedure are set out in theNotice to Applicants Volume 2C, “Guideline on the packaging information of medicinal products for human use authorized by the Community”.

Blister Pack Presentations	Apply the batch number and expiry date to the end of the blister strip. If technically possible, applying this information to both ends of each strip should be considered. Where a unit-dose blister presentation is proposed all the information required for blister packs must appear on each unit dose presentation.
Small Containers	Article 54 of Directive 2001/83/EC and article 55 gives the label requirements. The criteria for small container status would normally apply to containers of nominal capacity of 10ml or less.

Table 5: TGA Expression of quantity or proportion of active ingredient in Medicines

Dosage Form	Requirements
Discrete dosage unit	Quantity of the active ingredient in the dosage unit.
Liquid for ingestion	Quantity of the active ingredient contained in the stated volume of a suitable dose of the liquid.
Solid for ingestion	No discrete dosage unit - as the quantity of the active ingredient contained in the stated weight of a suitable dose of the solid.
Transdermal patch	As the quantity of the active ingredient released in a stated time.
Homoeopathic preparation	The quantity of the ingredient in one milliliter or in one gram of the preparation. Expressed as 'Contains equal parts of' followed by the name of each homoeopathic ingredient.
Preparation for injection Volume in the container is 1 milliliter or greater Volume in the container is less than 1 millilitre Small volume injection Large volume injection	The nominal quantity of the active ingredient in the container. The quantity of the active ingredient in one milliliter of the injection. The quantity of the active ingredient in a suitable dose volume of the injection. The quantity of active ingredient in the stated volume of the injection in the container. The weight of the active ingredient in the stated volume of injection in the container.
Antibiotic preparations	Potency units are used as a measure of activity expressed as International Units (IU).
Topical preparations	Percentage expressed in terms of w/w, w/v, v/v or v/w, as appropriate, or as the weight or volume in a stated weight or volume of the goods, as appropriate.
Herbal substance preparations	The quantity of the herbal substance in the preparation or the quantity of the raw material herb used to make the ingredient expressed as the equivalent dry or fresh weight; or the quantity of the raw material juice used to make the concentrate or dilution expressed as the equivalent dry weight, fresh volume or fresh weight.
Mineral supplement preparations	Quantity of the element with the name of the salt being indicated.
Vitamin A preparations	The quantity or proportion of Vitamin A expressed in terms of retinol equivalents (R.E.)
Pressurised metered dose inhalers and dry powder inhalers	The powder for inhalation is supplied as a single dose in a capsule, or as a well in a blister tray or other suitable pharmaceutical form – as the quantity of active ingredient in each dosage unit.
Preparation containing biological organisms	The number of organisms present per metric unit for liquids and powders and as the number per dosage unit for other dosage forms.

4. Conclusion

Regulatory affairs are rewarding, intellectually stimulating and highly regarded profession with in pharmaceutical companies. Every country has its own regulatory agency and guidelines to be followed. These guidelines are specified based on their human need, environment conditions and some laws. Most of the guidelines in packaging and labelling concern are similar, but differs in few aspect.

5. References

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[5] FDA Guidance for Industry on the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use (August 1996).

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