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Essentials of pharmaceutical packaging to prevent drug counterfeiting

RAKESH NALAM *

Andhra Pradesh, India.

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Abstract

The purpose of this paper is to explain the process for pharmaceutical drug packaging with serialization regulatory requirements. Generally, pharmaceutical packaging deals with the labeling and packing of products including injectables, tablets, pills, and other forms of medication. It is essential to maintain the quality and safety of the product from the manufacturing site to the customer. When it comes to labeling, it provides identification for the product, such as dosage, strength, and name, and in packing, it secures the product from physical damage, contamination, and degradation. During the packing of products, there will be a set of standards to be maintained, such as GxP standards. The FDA has released some guidelines to be followed with the packaging of pharmaceutical products. Serialization is an additional mandatory requirement for the prescribed products to secure drugs from falsification and counterfeiting throughout the supply chain.

Keywords: Pharmaceutical packaging; Pharmaceutical Serialization; Contamination; GxP standards; FDA

1. Introduction

Basically, pharmaceutical products should be handled with the utmost care because they are lifesaving products. Therefore, manufacturing and packaging of medical products will be carried out in a very hygienic area with standard operating procedures to avoid contamination and product mix-ups. These manufacturing areas are classified into two types: classified areas and unclassified areas. Drug preparation and filling come under classified areas, and inspection and packing will be treated as unclassified areas. The product, formula, treatment, or therapy is controlled and endorsed by a foreign equivalent of the Food and Drug Administration (FDA), which investigates and tests products or services developed, manufactured, or distributed by a company or any of its subsidiaries.

Global healthcare businesses profited from technological advancement and greater globalization of pharmaceutical commerce [1]. Critical medications are now easier to obtain and can be purchased from reliable sources. Additionally, it gives drug traffickers and counterfeiters a chance to sell drugs on dark-web sites and social media [2]. People are drawn to buying medicines online for a variety of reasons, including geographic restrictions, lower prices, quick time to market, direct client targeting, and more customer reach [3].

Even though the packing area is an unclassified area, the criticality should be high as well as compliance with regulations and industry standards. It is important for manufacturers to follow best practices and guidelines for labelling and packing to ensure that products are accurately identified, tracked, and delivered to the end consumer in a safe and timely manner. Since it's estimated that 50 percent of pharmaceutical recalls are due to errors in product labelling or packaging artwork, To overcome all this, the FDA has announced draft guidance specifying the way manufacturers are required to label their pharmaceutical products. These regulations were put in place in order to protect the consumer and standardize the packaging industry. Packaging is a science that is continuously evolving and is a major success

* Corresponding author: Rakesh Nalam; E-mail: rakesh.nalam97@gmail.com

factor for the pharmaceutical industry [4]. Pharmaceutical packing varies from drug to drug, but normally there are three levels of packing: primary packing, secondary packing, and tertiary packing [5, 6].

1.1. Primary packing

The primary packaging system is the material that first envelops the product and holds it, i.e., those package components and subcomponents that actually come in contact with the product, such as glass or plastic vials, ampoules, blister packs, and pre-filled syringes [7]. The choice of primary packaging material depends on the product's characteristics, such as its physical and chemical properties, stability, and shelf life, as well as regulatory requirements.

Figure 1 Primary Packaging Types

1.2. Secondary packing

It is packaging that contacts primary packaging and provides additional support, protection, and identification to the product, such as cartons, trays, labels, shrink-wrap, partitions etc.

Figure 2 Secondary Packaging Types

1.3. Tertiary packing

It is the packing that gives support to the secondary packing, and it is the outermost layer of the packing, such as boxes, shippers, pallets, etc. It is designed to protect the product from damage during transportation and distribution. [8].

Figure 3 Tertiary Packaging for serialized shipper case

2. Essential requirements for labelling and packing

While packing there should be mandatory requirements to be followed while designing of area and Equipment and also set of procedures to be followed while packing the product.

- **Monitoring of Temperature:** Temperature should be a major consideration while packing. Excessive temperature will cause the person discomfort and can increase microbial growth. The most stable temperature in packing is 15°C to 25°C, and it should be monitored by data loggers or temperature sensors.
- **Compliance with regulatory standards:** Pharmaceutical packing lines must adhere to strict regulatory standards set by organizations such as the Food and Drug Administration (FDA) or equivalent regulatory bodies in different countries. These standards encompass areas such as product safety, quality, and labelling requirements.
- **Cleanroom Environment:** Pharmaceutical packing lines typically operate in cleanroom environments with controlled air quality, temperature, and humidity. These conditions help minimize the risk of contamination and ensure the integrity of the packaged products.
- **Validation and Qualification:** Pharmaceutical packing lines must undergo validation and qualification processes to verify their performance, accuracy, and reliability. This includes equipment qualification, process validation, and documentation to ensure that the packaging line consistently produces conforming products.
- **Documentation and Batch Records:** Detailed documentation and batch records should be maintained throughout the packaging process. This includes recording critical process parameters, equipment settings, batch numbers, product identification, packaging materials used, and any deviations or interventions during the process. Accurate documentation facilitates traceability and regulatory audits.
- **Good Manufacturing Practices (GMP):** Compliance with GMP guidelines is crucial for pharmaceutical packaging. GMP covers various aspects, including personnel hygiene, equipment cleanliness, documentation, quality control, and traceability. Adhering to GMP ensures the production of safe and high-quality pharmaceutical products.
- **Track and Trace Systems:** Pharmaceutical packaging lines should incorporate track and trace systems to enable accurate identification, serialization, and tracking of individual products throughout the supply chain. These systems aid in product authentication, anti-counterfeiting measures, and recall management.
- **Machinery:** The packing lines includes specialized pharmaceutical equipment's for smooth and reliable operation. This may consist of labelling machines, coding machines, inspection system to ensure providing proper identification of product.
- **Safety and Hygiene:** The packing line should prioritize employee safety and hygiene. This may involve implementing safety features on equipment, providing appropriate personal protective equipment (PPE), and ensuring proper sanitation and cleanliness throughout the facility.

3. Importance of labelling and packing

We are all aware of how packaging helps identify and protect the product. Packaging must provide protection, identification, and information against physical damage, loss of content or ingredients, and intrusion of unwanted components of the environment such as water vapor, oxygen, and light [9]. When it comes to pharmaceutical drugs, they play a crucial role because they deal with human life sensitively, and in other words, they protect the drug from damage and mix-ups and help it reach the patient safely. Packaging materials are very sensitive for drug authentication and needs investment. Generally small manufacturers find it difficult to invest in new machinery and printing equipment's. [10, 11, 12]. When it comes to labeling, initially the drug has no identification. No one can identify what it contains or how much dosage it contains [13]. In the stage of labeling, we are giving a name and identity to the product, so it gives clear information about how to use it. We are providing labeling with a set of information like product name, dosage, strength, batch number, expiration date, and some other information that is required by the regulatory body [14]. When it comes to packing, the major aspect is to protect the drug from damage during loading and transport, as well as from physical conditions like temperature, humidity, vibrations, mechanical shocks, and electrostatic discharge. And it also acts as security for the product, reducing the risk of theft and mix-ups. And it will add convenience to distribution, handling, and dispensing [15].

Another important aspect of labeling is promoting the brand name. Labels and packaging contribute to the branding and marketing efforts of pharmaceutical companies. A well-designed label can help differentiate a product from competitors and create brand recognition [16]. It can convey professionalism, trustworthiness, and quality. Packaging design also plays a role in the perception of the product and can influence a patient's or healthcare professional's decision to choose one brand over another. Similar important activity that takes place in the packing area is serialization,

which helps to trace the product and minimize counterfeits and tampering. It is one of the regulatory requirements that all countries need to follow as per the standards. It serves as a unique identifier for each product. Properly labeled products enable traceability throughout the supply chain, making it easier to track and recall specific batches or lots in case of quality issues or safety concerns. Pharmaceutical packaging errors such as incorrect labeling and improper packing can lead to serious side effects, premature spoilage, cross-contamination, consumer illness and fatalities, and costly recalls and fines. As per records, 60% of recalls were due to labeling errors and packaging artifacts, and on average, 25% to 50% of total recalls were due to human error. Simple errors like incorrect data selection, spelling mistakes, and misplacement of products in packing lines have a major impact on patient life and company reputation.

4. Different types of pharmaceutical packings

Majority of medicines have been taken orally trough capsules or tablets which is either packed in blister packs or aluminum strips. However, other methods for taking medicines are now being more widely used which include parenteral or intravenous, inhalation, and transdermal methods.

4.1. Vial or Bottle packing

It is tough, transparent glass or plastic that can be availed in different sizes like 10 mL, 20 mL, 50 mL, 100 mL, etc. It will be sealed with a sterile rubber stopper followed by an aluminum seal, which helps block the air from passing from outside. And it also protects from temperature, light, and atmospheric conditions. There are some products that may change their properties when they come into contact with light. In such conditions, we use transparent amber glass, which protects the drug from light. And the labeling was done on the outside of the bottle, and the bottles were packed into trays, followed by the shipper.

4.2. Ampoule packing

It is a sealed, transparent glass container filled with drugs. After filling the tube with the solution, it passes through a sealing station where it can be sealed with heat. And it contains color-coded rings around their necks, which are an identification for breaking an ampoule. The labeling was done on the body of the ampoule, and later it was placed in protected shells to prevent breakage. These are available in only small sizes, like 1 mL to 30 mL. Glass ampoules have been criticized due to the inherent risk of small glass shards entering the fluid and being administered to a patient intravenously.

4.3. Blister or Strip Packing

The drug is compressed into solid form and packed as tablets or capsules. These pills are distributed in blisters, aluminum strips, or thermoplastic sheets. All the drug information was printed on these sheets, along with the batch number and expiration date. Blister packs are light and cheap and can be carried and consumed very easily and safely.

4.4. Sachet Packing

These are available in small pouches with different shapes and sizes, like rectangles and squares. If the drug is in the form of a solid or powder, this packaging will be preferred. These are usually made of a paper-plastic combination that can be torn easily with the hand. The product information is printed on these sachets. These pouches are affordable and can only be used once, as once torn, they can't be reused.

5. Characteristics of packing material

Package design and construction play a significant role in determining the shelf life of food as well as pharmaceutical products. The materials used for labeling and packing will play a crucial role in drug manufacturing and delivery. The right selection of packaging materials maintains product quality, stability, and freshness during distribution and storage. Some of the materials, like vials, ampoules, and stoppers, will directly contact the drug, so the drug should not change its properties with these materials, and some, like labels, trays, and cartons, should protect the drug from contamination and damage and provide accurate information about the drug. And all these materials should be inspected and certified by a quality authority for further use. For this, we should consider some characteristics before selecting the material [17].

- The materials should be Approved by the respective regulatory authority.
- It should be Non-toxic in nature.
- It should not have any impact on the product properties like color, taste, odor, etc.

- It should not be reactive to the product.
- The material should protect the drug from environmental conditions during manufacturing and transportation.
- Reusable/recyclable
- Effective, cost-effective, and easy to use.

Every pharmaceutical manufacturing site will have some Standard operating procedures, which will depend on the commitments that they have made to the regulatory authority.

6. Verification of barcode in the packaging

Barcode verification basically reduce the danger of illegal and counterfeit pharmaceuticals entering the market by implementing digital tracking of pharmaceutical drugs in the supply chain [18] recommended placing special 2D barcodes on every prescription box to make scanning easier and display the medication's history and other vital details [19].

Consider a different kind of barcode called a 2D data matrix, which can record electronically encoded data like a producer ID, product ID, or a distinctive ID frequently used on medication containers. Government regulatory agencies and parties in the pharmaceutical supply chain have grown noticeably more watchful of suspected and counterfeit medications since 2018. Due to regressive digital verification and validation processes throughout the entire supply chain, the European Union has been successful in reducing suspected product alerts. According to the DSCSA 2023 Act, every trade partner in the supply chain, including the dispenser and pharmacy, shall be able to confirm a fictitious or dubious product identifier upon request from another trading partner, a regulatory body, or any state agency [20].

7. Regulatory requirement of packaging

It is advised to have an interpretation of the application identifiers (AIs) and the data they are connected with that is human readable. close to the GS1 data matrix symbol that contains the encoding. The individual application standards specify the exact position and typeface to be utilized for the human-readable Interpretation. The important data, like the Global Trade Item Number (GTIN), is typically placed in the human-readable data underneath the barcode. However, the characters must be distinctly readable and must be connected to the symbol in a clear way. In order to facilitate key entry in the event that the symbol cannot be scanned, Application Identifiers (AIs) should be easily discernible within the human-readable interpretation. The AI is enclosed in parenthesis to accomplish this. The parenthesis is not encoded in the symbol or included in the data. This stands in stark contrast to the use of the FNC1, which, when used as a start or separator character, must be encoded in the symbol but never occurs in the human-readable interpretation.

8. Emerging technologies for drug packaging

8.1. Authentication technique

The process of verifying or confirming something's authenticity is known as authentication. Since the use of fake medications can be detrimental to patients' health and wellness, authenticity is crucial. Utilizing them could lead to treatment failure or even death [21].

8.2. Overt (Visible) Features

Users are anticipated to benefit from overt elements that help them verify a pack's authenticity. Such qualities will be very noticeable and difficult or expensive to duplicate [22]. Barcodes are two-dimensional or linear high-density codes applied to product packaging that are scanned and transmitted to a central database. Two-dimensional barcodes and high-quality tiny images can both be created using laser technology. To create a legible depiction, users must ensure that the print contrast between the light and dark bars is sufficient.

8.3. Central Database for authenticating packages

Pharmaceutical drugs are essential for human life. Barcodes on drug packages are essential for preventing drug counterfeiting. Europe is using a centralized database for authenticating drugs in the supply chain. Numerous studies have indicated that 2D barcodes embedded on drug packaging mitigate 90% of drug counterfeiting in the supply chain [23]. By individually coding each package, as is the case in EU nations, an automatic drug tracking system should be an efficient part of halting the proliferation of fake medications [24]. With the help of blockchain technology, you can track the chain of supply. Information is recorded in the blockchain from the point of release until it enters the retail network.

You can then add functionality to this system, such as the ability to control the drugs in medical facilities. The conditions of storage of medicinal products during their delivery (temperature regime) are also monitored [25]. On a blockchain platform, blockchain technology, with an emphasis on cost and safety, may help pharmaceutical cold chains and fight medicine counterfeiting. To address the issue of data storage, blockchain platforms can interact with cloud storage components. Blockchain is capable of merging massive heterogeneous data generated from various sources in order to effectively trace drug fraud. [26]. The ability to trace down anything at any time, including medical supplies, prescriptions, and even the monitoring of temperature in the pharmaceutical supply chain, is made possible by blockchain technology. The data in every transaction uploaded to the blockchain platform in the drug supply chain can be tracked at any time by the authorized parties. Decentralized storage, which keeps several versions of the data in many locations based on allowed stakeholder authorization, is one of the key potentials that would be able to change the healthcare business with the integration of blockchain [27].

9. Conclusion

Pharmaceutical packages play a crucial role for drug security in serialization procedures. The DSCSA required manufacturers to include a 2D Data Matrix symbology barcode and uniform case labels on their products in order to make them internationally compliant with the supply chain's serialization requirements. The DSCSA also required the printing of GS1-2D Data Matrix barcodes next to human-readable forms that adhered to the norms established by a well-known international standards development organization. The serialized data encoded in barcodes harmonizes supply chains in global trade, making it simpler and more reliable to read data using radio frequency equipment. Because the serialization label contains a unique product identity, the barcodes reduce the possibility of counterfeiting as well. According to the DSCSA, a product's identifier must be a "standardized graphic that includes, in both machine-readable form and on a widely acknowledged international standards development organization's standards, the standardized numerical identifier, lot number, and expiration date of the product." To increase product security along the supply chain, additional medicine packaging should have temper evident added. The DSCSA has mandated that serialization data be transmitted electronically and in an interoperable way by manufacturers, wholesalers, and distributors, where barcodes on pharmaceutical supply chains will play a crucial part in reducing the danger of medication counterfeiting. In order to reduce the danger to patients' health from pharmaceutical errors, barcode labeling can be crucial. It is important to carefully insert the barcode on the medication because any errors could trigger batch recalls and further inquiry as well as confusion and delays in the supply chain.

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