SunChemical®
a member of the DIC group
Color & Comfort

Legislation – Pharmaceuticals – Information

Packaging is an integral part of a pharmaceutical product. Pharmaceutical packaging is highly regulated but with some variation in the details, depending on the country of origin or region. Several common factors can include: assurance of patient safety, assurance of the efficacy of the drug through the intended shelf life, thorough documentation of all materials and processes, control of possible migration of packaging components into the drug, control of degradation of the drug by oxygen, moisture, heat, etc., prevention of microbial contamination, sterility, etc. Packaging is often involved in dispensing, dosing, and use of the pharmaceutical product. Communication of proper use and cautionary labels are also regulated. Packages often need to have tamper resistant features and child-resistant packaging.

Packaging preserves the stability and quality of medicinal products and protects them against all forms of spoilage and tampering. All medicinal products need to be protected and consequently need to be packaged in containers that conform to prescribed standards, particularly with respect to the exclusion of moisture and light and the prevention of leaching of extractable substances into the contents and of chemical interaction with the contents. Packaging materials include printed material employed in the packaging of a pharmaceutical product, but not any outer packaging used for transportation or shipment. All finished drug products should be identified by labelling, as required by the national legislation.

The materials used in pharmaceutical packaging are crucial for ensuring that the product remains free of contaminants. The type of material used depends on which category of pharmaceutical packaging is required. The container and its closure must not interact physically or chemically with the substance within in any way that would alter its quality.
The requirements to be met by pharmaceutical packaging and packaging materials as described in compendia (pharmacopoeias) and standards (e.g. those of the International Organization for Standardization (ISO)) must be considered only as general in character. The suitability of packaging or packaging material for any particular requirements and conditions can only be ascertained through detailed packaging and stability studies on the product concerned.

Pharmaceutical packaging is essentially split into three different formats. Each of these has different demands placed on the materials and design used.

Primary packaging
Primary packaging is when the pharmaceutical comes into direct contact with the container. For this reason, primary packaging should be inert so that it does not react with the product inside. Examples include a polymer or cold form blister or bottle for tablets, a vial or syringe for sterile liquids, or a tube for a dermatological cream, and an aluminium can for an inhaler. Primary packs are typically labelled/coded with information such as batch number, product, expiry date, etc.

All these formats must undergo stability testing to ensure that the sealed primary pack meets an appropriate shelf life (typically 24-36 months) to offer robustness in the supply chain and also that there is no impact from material/medicine interaction – via extensive extractables and leachables testing. Safety attributes, such as child-resistant features, can be added to the primary packaging (and secondary packaging) as required. C*ommon types of material used for primary pharmaceutical packaging include glass, thermoformed products and stainless steel.*

Secondary packaging
Secondary packaging is when the pharmaceutical product does not come into direct contact with the container. Most medicine primary packs are placed into secondary packs. These are typically cartons but also extend to devices such as inhalers and injectors, which themselves are then placed into cartons. Additional secondary packaging may also be added to offer enhanced protection, and these can include preformed polymer trays or foil overwrap.

Secondary packs are printed and labelled, and extensive transit testing is undertaken with finished packs to ensure that they are robust. The type of material used in secondary packaging is less important since there will be only a small risk of contaminating the product. Patient Instruction Leaflets (PILs) are also included with every pack as these are a regulatory requirement in many markets.

Tertiary packaging
Tertiary packaging is used in factories to protect the product during storage or transit. This includes shipping cases, pallets, shrink wrap and specialist formats – for example, those used in the cold chain – which is required for some medicines, such as vaccines.

The complexity of packaging materials and the highly technological nature of medicinal products is such that manufacturers can be confronted with significant problems. Interaction between packaging and such products is possible due to the combination of a multiplicity of container components and active pharmaceutical ingredients, excipients and solvents used in a variety of dosage forms. The quality of the packaging of pharmaceutical products plays a very important role in the quality of such products. It must:

- **protect against all adverse external influences that can alter the properties of the product, e.g. moisture, light, oxygen and temperature variations**
- **protect against biological contamination**
- **protect against physical damage**
- **carry the correct information and identification of the product**

The kind of packaging and the materials used must be chosen in such a way that:

- **the packaging itself does not have an adverse effect on the product (e.g. through chemical reactions, leaching of packaging materials or absorption)**
- **the product does not have an adverse effect on the packaging, changing its properties or affecting its protective function**

The resulting requirements must be met throughout the whole of the intended shelf-life of the product. Given the link between the quality of a pharmaceutical product and the quality of its packaging, pharmaceutical packaging materials and systems must be subject, in principle, to the same quality assurance requirements as pharmaceutical products.

Substances and dosage forms requiring protection from light should be maintained in a light-resistant container that - either by reason of the inherent properties of the material of which it is composed, or because a special coating has been applied to it - shields the contents from the effects of light. Alternatively, the container may be placed inside a suitable light-resistant (opaque) covering and/or stored in a dark place. Prescription bottles come in several different colours, the most common of which being orange or light brown due to its ability to prevent ultraviolet light from degrading the potentially photosensitive contents through

photochemical reactions, while still letting enough visible light through for the contents to be easily visible.

The containment of the product is the most fundamental function of packaging for medicinal products. The design of high-quality packaging must take into account both the needs of the product and of the manufacturing and distribution system. This requires the packaging:

- **not to leak, nor allow diffusion and permeation of the product**
- **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**

The packaging must protect the product against all adverse external influences that may affect its quality or potency, such as:

- **light**
- **moisture**
- **oxygen**
- **biological contamination**
- **mechanical damage**

While excluding the effect of external factors on the product, the packaging itself should not interact with it so as to introduce unacceptable changes. There are numerous possibilities of interactions between (primary) packaging materials and pharmaceutical products, such as:

- the release of chemicals from components of the packaging materials
- the release of visible and/or subvisible particles
- the absorption or adsorption of pharmaceutical components by the packaging materials
- chemical reactions between the pharmaceutical product and the packaging materials
- the degradation of packaging components in contact with the pharmaceutical products
- the influence of the manufacturing process (e.g. sterilization) on the container

The active pharmaceutical ingredients should remain within their specification limits over the shelf-life of the pharmaceutical product. The question of whether a packaging will provide the required protection for the pharmaceutical product and the required stability over a certain time period can only be answered by means of real-time stability studies. Such studies must evaluate the changes in the quality of the product, in contact with its packaging, during a period equivalent to its intended shelf-life. In addition, packaging must meet the following requirements:

- it must preserve the physical properties of all dosage forms and protect them against damage or breakage
- it must not alter the identity of the product
- it must preserve the characteristic properties of the product, so that the latter complies with its specifications
- it must protect the product against undesirable or adulterating chemical, biological or physical entities

Pharmaceutical packaging is part of the pharmaceutical drug registration. The requirements depend on the risk class of the end application. Primary packaging i.e. plastic containers for

pharmaceutical purposes intended to hold medicinal products are or can be in direct contact with pharmaceuticals. The closure is part of the container. Such plastic containers can be made from materials with certain additives. Types and quantities of additives depend on the types of polymers used, production processes and intended purpose of the container. Relevant descriptions are provided in the Pharmacopoeia. In secondary packaging, the packaging does not come into direct contact with packed pharmaceuticals or drugs. In this case, materials used for secondary packaging are not subject to any official legal requirements or recommendations.

Packaging is also an essential source of information on medicinal products. Such information is provided by labels and package inserts for patients. Specifications for labels for finished drug products are defined in the WHO guidelines on GMP for pharmaceutical products.

All aspects of pharmaceutical production, including packaging, are tightly controlled and have regulatory requirements. Uniformity, cleanliness (washdown), sterility, and other requirements are needed to maintain Good Manufacturing Practices. Product safety management is vital. A complete Quality Management System must be in place. Validation involves collecting documentary evidence of all aspects of compliance. Hazard analysis and critical control points is a methodology which has been proven useful. In the manufacture of pharmaceutical products, quality assurance is defined as the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use. Quality assurance extends beyond the packaging operations through distribution and cold chain management; good distribution practice is often a regulatory requirement and track and trace systems are usually required.

Medical devices
A medical device is an instrument, apparatus, in-vitro agent, etc., used to diagnose, prevent or treat disease or others. The medical device application is highly regulated and varies globally from jurisdiction. The requirements depend on the risk class of the end application. The approval of the end application requires a considerable amount of data and safety assessments. In the EU, all medical devices have to be identified with the CE mark.

Further information

World Health Organization WHO Technical Report Series, No. 902, 2002
Annex 9 Guidelines on packaging for pharmaceutical products
https://www.who.int/medicines/areas/quality_safety/quality_assurance/GuidelinesPackagingPharmaceuticalProductsTRS902Annex9.pdf

Requirements regarding the quality of pharmaceutical packaging are specified in the European Pharmacopoeia (Ph. Eur., 10th edition 2020).
https://www.edqm.eu/en/european-pharmacopoeia-ph-eur-10th-edition

PS 9004 A Guide to the GMP requirements of PS 9000:2001 Pharmaceutical packaging materials
https://www.pharmamanufacturing.com/assets/Media/MediaManager/cGMP_complete.pdf

EMEA Guideline on Plastic Immediate Packaging Materials
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-plastic-immediate-packaging-materials_en.pdf

The information contained herein is based on data believed to be up-to-date and correct at the time writing. It is provided to our customers in order that they are able to comply with all applicable health and safety laws, regulations, and orders. In particular, customers are under an obligation to carry out a risk assessment under relevant Good Manufacturing Practices (GMP) in line with legislation and as a result take adequate measures to protect consumers.