Avery Dennison
Label and Packaging Materials
Compliance & Reference Guide

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Pharmaceutical Package Labeling

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Ensuring patient safety through compliance

In the pharmaceutical world, packaging plays a pivotal role in delivering life-saving medicines and ensuring the utmost safety of patients. The industry faces increasingly strict regulations, prompting the development of innovative materials tailored to the specific demands of the pharmaceutical sector. This focus extends beyond materials, encompassing adherence to quality standards, change management procedures, and personalized testing.

Standards and protocols are set by leading global organizations such as the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), and the International Organization for Standardization (ISO, who work diligently to ensure product safety and superior quality.

An overview of compliance standards

Pharmaceutical packaging

The safety of pharmaceutical packaging depends on its interaction with the product, requiring a comprehensive assessment of the fully assembled package, including labels. Evaluations of individual components like label materials and bottles are crucial for packaging engineers, informing the material selection for drug packaging and medical devices.

Regulatory and compliance considerations when choosing labeling material

Depending on the type of packaging and its specific end-use, various regulations and guidelines come into play. This guide provides a breakdown of the applicable standards for different packaging categories, including those used for drugs, medical devices, secondary packaging, and more.

The following table provides an overview as to what these standards are and where you can locate them throughout this reference and compliance guide.

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Medicinal (drug) product packaging

- Regulation (EC) 1935/2004 food contact materials

In the US (for high-risk medicinal products):

- US Pharmacopeia (USP 1663) - assessment of extractables associated with pharmaceutical packaging/delivery systems

In the US (for low-risk medicinal products):

- FDA 21 175.105

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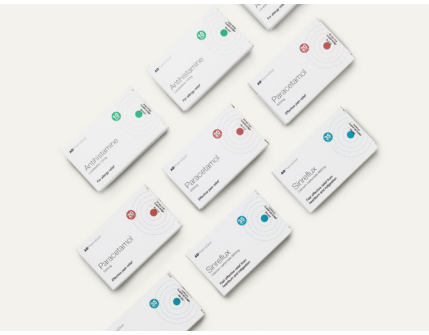
Medical devices

- Regulation (EU) MDR 745/2017

Standard(s) and guideline(s):

- ISO 10993-1: biological evaluation of medical devices
- ISO 10993-18: chemical characterization of medical device materials within a risk management process (extractables)
- ISO 10993-5: tests for in vitro cytotoxicity
- ISO 10993-23: tests for skin irritation
- ISO 10993-4: a selection of tests for interactions with blood



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Secondary packaging and cardboard boxes

- Falsified Medicines Directive (FMD) 2011/62/EU

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Other regulations and considerations

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Packaging for medicinal products

Packaging for medicinal products must meet certain standards. For example, in the EU, this will be the Guideline on Plastic Immediate Packaging Materials (Rules Governing Medicinal Products 3AQ10a) from the European Medicines Agency through the Committee for Medicinal Products for Human use (CHMP) and the Committee for Medicinal Products for Veterinary use (CVMP). There is also common guidance in the US by the FDA, namely the Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics.

Regulation (EC) 1935/2004 food contact materials

In the EU, food contact materials are regulated under 1935/2004/EC. Beyond this general legislation, there are specific legislations targeting particular materials. For instance, the Regulation (EU) 10/2011, commonly called the "plastic regulation" stands as a vital means of ensuring the safety of plastic materials through migration limits. These limits dictate the utmost quantity of substances permitted to migrate to food.

For substances detailed on the union list, the regulation establishes 'Specific Migration Limits' (SML). The EFSA determines each SML based on the toxicity data of the individual substance in question. Upholding the overarching quality of the plastic, the cumulative migration of all substances to food must not surpass the Overall Migration Limit (OML) of 60 mg/kg food, as outlined by the European Commission.

Although food contact approval cannot substitute regulatory qualification for medical devices or drug packaging in the EU, it can be used as a reference when evaluating the appropriateness of label materials in drug packaging In the EU, food contact approval isn't enough for drug packaging conformity. Medium and high-risk packaging must undergo extractables and migration studies, while low-risk packaging needs general specification and interaction studies.

US Pharmacopeia (USP 1663)

In the US, packaging conformity assessments for medicinal products vary by risk level. Low-risk packaging like oral tablets and capsules not for chronic use requires only a reference to indirect food additive regulations. However, medium and high-risk items, such as sterile powders for injection, injectable suspension, ophthalmic solutions, transdermal ointments, and nasal aerosols/sprays, need extractables and leachables studies per US Pharmacopeia (USP) 1663.

FDA 21 175.105

The Food and Drug Administration (FDA) is the US federal agency that safeguards public health. It accomplishes this by ensuring the safety, efficacy, and security of human and animal medications, biological products, and food. Within the Code of Federal Regulations 21 lies section 175.105, which pertains to "indirect food additives: adhesives." This encompasses a roster of specific chemical substances permitted for adhesive use when a functional barrier exists between the medicine and the adhesive. The principal aim of FDA 175.105 is to guarantee that unapproved substances avoid contact with food. Furthermore, it ensures that adhesives are employed safely in food applications, thereby maintaining food safety for consumption. As previously stated, compliance with this regulation can only be claimed for drug packaging of low-risk and only in the US.

Medical devices

Our labels can also be attached to medical devices. Medical devices are instruments, apparatus, appliances, software, implants, reagents, materials, or other articles, alone or in combination, intended for medical purposes. This is specified within the scope of Regulation (EU) 745/2017 on medical devices. Although our labels are not medical devices by themselves, they become subject to the overall assessment of the medical device when applied in its final form.

Medical devices are classified based on their risk during use and divided into classes I, IIa, IIb, and III, with some labels on high-risk items like blood bags with heparin falling under class III. The risk class determines the EU conformity assessment needed to ensure safety and performance. Part of this assessment includes a biocompatibility study following ISO 10993 guidelines by the International Organization for Standardization (ISO), covering various biological effects and interactions, sample preparation, and additional evaluations.

ISO 10993-1: biological evaluation of medical devices

"Biocompatibility study is defined as an evaluation of the biological effects of compounds extracted from devices or the effect of direct interaction of the device with a surrounding tissue through in vivo and/or in vitro methods"[1]. The primary goals of conducting biocompatibility studies are to minimize risks during the pharmaceutical development process, demonstrate whether medical devices may cause any adverse physiological reactions, and ensure products are designed with safety in mind.

Biocompatibility studies focus on the device's contact type and duration with the body, falling into categories like surface medical devices, externally communicating medical devices, and implant medical devices. Most of our labels are externally communicating devices.

Per ISO 10993-1, four key endpoints must be evaluated for medical device safety: extractables and leachables (ISO 10993-18 & 17), in-vitro cytotoxicity (ISO 10993-5), skin sensitization (ISO 10993-10), and skin irritation (ISO 10993-23). Additionally, devices in contact with blood, as per ISO 10993-4, must meet a hemocompatibility endpoint.

1. *Biocompatibility and Performance of Medical Devices (second edition)*, 2020.

ISO 10993-18: chemical characterization of medical device materials within a risk management process

This standard outlines initial biocompatibility studies, including the chemical characterization of medical devices and identifying and quantifying chemical substances that may be released and come into contact with the body, focusing on two types of examination: extractables and leachables studies.

The extractables study aims to detect and measure potential contaminants from pharmaceutical packaging or medical devices, conducted under exaggerated 'worst-case scenario' conditions to prevent quality compromise and patient health risks. In label materials, extraction testing uses specific solvents under rigorous conditions, simulating real-world scenarios. For instance, ethanol at 50% v/v is used to mimic exposure to various organic substances and components.

In real-world applications, label materials rarely contact medicines directly or undergo extreme treatment conditions, making leachables studies more relevant. These studies identify and quantify substances that might migrate from labels under typical usage conditions over the product's lifespan. However, assessing only our labels isn't feasible, as testing parameters should be set by end-users in context with primary packaging and anticipated use conditions.

Further toxicological evaluation and risk assessment for leachables can be guided by the standards set in ISO 10993-17.

ISO 10993-5: tests for in vitro cytotoxicity

Cytotoxicity refers to the potential of certain substances to be harmful to cells, indicated by the inhibition of cell growth when incubated with these substances. To assess the cytotoxic effects of chemicals, two prevalent methods are employed: microscopy cell characterization (reactivity grading) and colorimetry based on dehydrogenase activity (XTT assay).

ISO 10993-23: tests for skin irritation

This describes the procedure to assess a regulatory endpoint aiming to identify chemicals able to elicit localized inflammatory responses to single, repeated, or continuous application of the test substance without involvement of an immunological mechanism.

ISO 10993-4: selection of tests for interactions with blood

This framework outlines procedures to evaluate the interaction between medical devices and blood, emphasizing the importance of materials and design being safe and non-reactive upon blood contact. It guides in selecting appropriate tests to assess this interaction, which, depending on the device's usage and blood contact level, may include Hemolysis tests, Partial Thromboplastin Time (PTT) tests, Thrombosis Assay, Complement Activation, and Leukocytes Activation assays.

ISO 3826-1, focusing on infusion equipment, highlights the importance of hemolysis (plasma hemoglobin) testing in medical devices with blood contact, as it evaluates red blood cell membrane fragility. Although this standard doesn't directly address label materials, it's relevant for considering their unintended chemical interactions with such equipment.

Hemolysis testing is essential for our labels on blood bags, but due to challenges in isolating the labels' impact and the variability of blood bag plasticizers, it's best performed by end-users in real-world applications. Thus, our labels' safety assessment shouldn't rely only on hemocompatibility endpoints but on specific use scenarios.

Secondary packaging and cardboard boxes

Although secondary packaging does not carry a high level of risk regarding topics like cytotoxicity and biocompatibility of migration, they need to adhere to guidelines that aim to ensure patient safety by mitigating the risk of drug falsification.

Falsified Medicines Directive (FMD) 2011/62/EU

This EU initiative was introduced to combat the rise of counterfeit medicines within the EU's pharmaceutical supply chain. Passed in 2011 and fully functional since 2019, the directive enforces strict criteria to authenticate prescription drugs. It achieves this by using unique identifiers and incorporating tamper-evident packaging for all pharmaceutical products. A prevalent form of such tamper-evident packaging is cardboard boxes equipped with a self-adhesive label that functions as a security seal.

In regards to the standard to conform with this directive, the NEN-EN 16679 outlines the requirements and offers guidance concerning the application, utilization, and verification of tamper-proof features on medicinal product packaging. While the ultimate FMD compliance hinges on the specific interplay between label material and product packaging, testing security seals on commonly used cardboard types and varnishes provides a reliable gauge of the material's performance.

Other regulations and considerations

In addition to the standard compliance requirements for pharmaceutical packaging outlined earlier in this brochure, selecting a labeling material demands extra attention. This is also true for other packaging components. These considerations are crucial for assessing risk, compiling documentation needed for marketing authorization, and ensuring the materials' safety.

Drug Master File (DMF)

A Drug Master File (DMF) is a document submitted to the US Food and Drug Administration (FDA). It provides a detailed and confidential account of the facilities, processes, or components involved in the manufacturing, processing, packaging, and storing of one or more human drugs. The data within a DMF can support various submissions, including an Investigational New Drug Application (IND), a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA), or even another DMF. Notably, the majority of our European pharmaceutical adhesives have DMF submissions.

In our case, type III DMF is most relevant, and the FDA uses our proprietary adhesive information to determine if this adhesive is safe to use in the applications of interest. Accordingly, the FDA will not disclose CAS numbers, safety data sheets, full material disclosures, and formulations to the end users.

Active substance master file

Similar to how DMF is used in the US, the European Medicines Agency has a similar system called Active Substance Master File (ASMF). ASMF can be used as an intermediate platform to share confidential information with the marketing authorization holder, allowing them to take full responsibility for the medicinal product and the quality control of the active substance. One of its contents pertains to packaging (including labels) as part of the container closure system. This particular section corresponds to the type III DMF.

REACH

REACH Regulation (EC) 1272/2008 is designed to improve the protection of human health and the environment by facilitating the early and enhanced identification of inherent properties in chemical substances. At Avery Dennison, as a downstream user of chemicals, we engage in close collaboration with our suppliers to uphold REACH compliance. This commitment encompasses continuous monitoring of the registration of all substances present in our products by our chemical suppliers and, when required, registering chemicals on our end.

PFAS

PFAS, or per- and polyfluoroalkyl substances, are often called “forever chemicals” because they persist in the environment and can accumulate in the human body. The European Union (EU) is actively tackling the issue through initiatives like the Chemicals Strategy for Sustainability, aiming to limit PFAS use in various products.

The European Chemicals Agency (ECHA) recognizes PFAS as a substance of very high concern, and potential restrictions are being considered. In regards to label materials, it is advised to check with the supplier whether PFAS is used in production processes or label materials itself.

Nitrosamines

Nitrosamines, chemicals with potential cancer-causing properties, were discovered in certain medicines, notably ‘sartans,’ in 2018. This issue was spotlighted by EU regulators when nitrosamine impurities, such as NDMA, were detected in blood pressure medications. By June 2020, the European Medicines Agency had completed a review providing guidance for marketing authorization holders in preventing nitrosamine impurities in human drugs, as per Regulation (EC) 726/2004. The EMA underscored instances where nitrosamines could stem from primary packaging, emphasizing the importance of thorough packaging risk assessment and investigation with the said regulation.

Natural Rubber Latex (compulsory in the US and guidelines for the EU)

The increasing incidences of allergic reactions to proteins in Natural Rubber Latex (NRL) highlight the need to ensure packaging materials do not cause these reactions. Consequently, the EC recommends that pharmaceutical and medical device manufacturers exclude such components from their products. This guidance extends to both packaging and labeling materials.


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Bringing it all together

Avery Dennison stands at the forefront of compliance management for pharmaceutical adhesives. With a team of experts, we ensure our products meet diverse requirements, delivering both change management and risk assessment services. Whenever changes arise, we evaluate their implications, produce in-depth documentation, and relay our findings to manufacturers and external partners.

Our commitment extends to ongoing product evaluations, aiming to deepen our insights into their effects on packaging and medications. The primary objective of our dedicated team is to remain ahead in this critical aspect, ensuring we provide unparalleled support to packaging engineers and those relying on our materials.

Guaranteed availability of pharma adhesives

- One year pre-notification time in case of modification*

Specific performance requirements

- Validated via application-based test methods

Change management control and supporting documentation

- Complete change management documentation
- Certificates
- Customized test reports
- Change notification statement /risk assessment
- Technical storyline and validation report

*Concerns adhesives S692NP, S2000NP, S717P, C2020P, C2050P, S2045NP, S2060NP, S799P, and S788P.

FAQ

Are some label materials safer than others?

The safety of labels hinges on the risk scenario. Since safety depends on the risk magnitude (combinations of hazard and exposure), the inherent properties of the labels only reflect the hazard. For instance, a label with 2% of toxic chemical Y is considered safer than one with 0.1% of the same chemical if the former is applied to functional glass barrier primary packaging. Conversely, the latter is used on permeable non-barrier LDPE packaging. Despite the higher concentration, the label with 2% toxic chemical Y is safer when applied to glass due to reduced exposure and migration risk into the container.

What are the potential risks associated with label materials that can impact drugs and patients?

There are two major risks related to the interaction between drugs and leachables and the inherent toxic properties of leachables. The first risk can result in reduced efficacy of the drugs and, subsequently the disease cannot be healed completely. Furthermore, if the by-products of interacting chemicals are also toxic, this can cause patient health concerns. As for the second risk, already harmful chemicals can also have a direct adverse impact on the patient's health.

Can we assume that all label materials that have "food contact approval" are also safe for pharmaceutical packaging?

For the EU market, food contact approval, according to EU 10/2011 and EC 1935/2004, cannot fulfill the safety screening for all drug packaging and medical devices. For medicinal products of high-risk and all types of medical devices, end users always have to proceed with extractables studies and other necessary biocompatibility assessments.

Avery Dennison:
Your Partner for Patient Safety

We have a wide range of tested, proven, compliant label materials for the pharmaceutical industry. With a solution for every application, we help manufacturers throughout the pharmaceutical industry track products, inform patients, and comply with regulations. And we want to work with you.

Who we are

As the pioneer in the pressure-sensitive industry, we bring one-of-a-kind capabilities to labels for the pharmaceutical and healthcare industry. We combine decades of innovation with deep knowledge of both regulatory and legal requirements. We know about the real-world conditions in which our labels must perform and the technical challenges they have to meet. Whatever your product, wherever it's going, we can help you develop a label that sticks with it.

What we stand for

Sustainability. Innovation. Quality. Service.

In 1935, we invented the first self-adhesive label, and we've never looked back. With each passing decade, our innovations have further shaped our industry by lifting the limits on what labels can do. The world's most successful brands know that innovation and evolution are the lifeblood of longevity and success. We're proud to help our clients continually expand the boundaries of what's possible.

Work with us

You're the expert in your business; we're the expert in pharmaceutical labeling. Contact your business development manager today to find out how Avery Dennison Pharmaceutical Labeling Solutions can meet and exceed your needs.

label.averydennison.com

For more information on technical performance and printing recommendations, please refer to the respective datasheets. Please note that the Avery Dennison product range and service offering can be subject to changes. For an accurate overview, please check our website label.averydennison.eu or contact your local Avery Dennison sales representative.

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