Pharmaceutical Package Labelling

Labels + Packaging
Compliance &
Reference Guide
Europe 2021

AVERY DENNISON

Compliance – it’s all about patient safety

Pharmaceutical packaging needs to comply with many regulations and fulfill numerous requirements.

When delivering life saving medicines patient safety is always at the center, medicines are subject to extremely stringent regulatory and compliance rules. This also applies to their packaging. Labeling materials that are meant for use in pharmaceutical packaging are subject to numerous compliance regulations and quality standards. At Avery Dennison, we offer a broad range of materials developed for one purpose: To meet the unique needs of the pharmaceutical industry. We are committed to fulfilling all regulatory compliance requirements and standards and go one step further by offering extensive change management procedure and customised tests and reports.

Regulations and guidelines across the globe
Organisations that contribute to generating the regulations and guidelines for pharmaceutical packaging include the European Medicines Agency (EMA), US Food and Drug Administration (FDA) and the International Organization for Standardization (ISO). These bodies oversee a wide range of regulatory mechanisms and standards, ensuring that products and services are safe, reliable and of good quality.

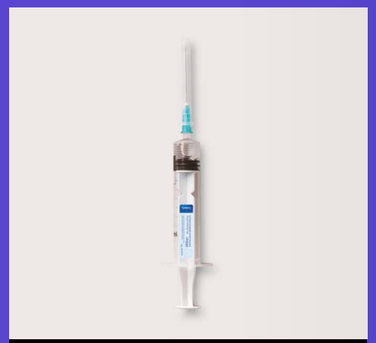
Regulatory and compliance considerations when choosing labelling material

Depending on the type of packaging and end application different regulations and guidelines are applicable:

Plastic containers

Pill, liquid medicine, eye drop bottles, blisters

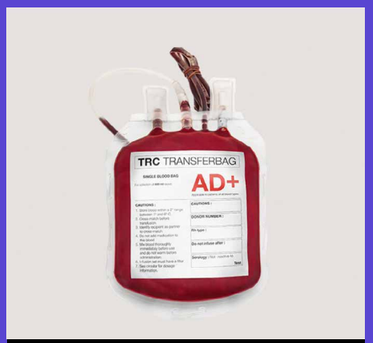
ISO 3826



Medical devices

Injectors, prefilled syringes, blood bag

ISO 10993 -5
ISO 10993 -17



Blood collection containers

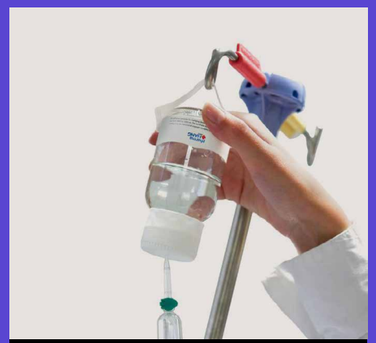
Blood bags

ISO 3826
ISO 10993

Prescription medicines

Secondary packaging, cardboard boxes

Falsified Medicine Directive 2011/62/EU



Functional packaging

Self-adhesive hanging devices, infusion bottles

ISO 15137
ISO 15010
DIN 58369

1935/2004/EC, FDA 175.105

The European Medicines Agency is issuing a variety of guidelines on packaging requirements and testing methods in relation to different European regulations and risks emerging on the market.

Other regulations and considerations

Drug Master File (DMF)

A Drug Master File (DMF) is a submission to the Food and Drug Administration (FDA) in the US that may be used to provide confidential detailed information about facilities, processes, or components used in the manufacturing, processing, packaging, and storing of one or more human drugs. The information contained in the DMF may be used to support an Investigational New Drug Application (IND), a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA) or another DMF. The majority of our European pharmaceutical adhesives are submitted to the DMF, meaning that our customer and their customers can request an authorization letter from Avery Dennsion to gain access to our submission to use it for their analysis and DMF application.

REACH

REACH (EC 1907/2006) aims to improve the protection of human health and the environment through the better and earlier identification of the intrinsic properties of chemical substances. As a downstream user of chemicals Avery Dennison collaborates closely with all suppliers to maintain REACH compliance. This includes ongoing monitoring of registration for all substances in our products by our chemical suppliers, as well as registering chemicals where necessary.

ROHS

The RoHS Directive aims to prevent the risks posed to human health and the environment related to the management of electronic and electrical waste. It does this by restricting the use of certain hazardous substances in EEE that can be substituted by safer alternatives (European Commission). All Avery Dennison Label and Packaging Materials EMENA's products currently in production are in compliance with the requirements of ROHS and its amendments.

Nitrosamines

Nitrosamines are chemical compounds classified as probable human carcinogens on the basis of animal studies. EU regulators first became aware of nitrosamines in medicines in mid-2018 when nitrosamine impurities, including N-nitrosodimethylamine (NDMA), were detected in blood pressure medicines known as 'sartans'. In June 2020 EMA finalised a review under Article 5(3) of Regulation (EC) No 726/2004 to provide guidance to marketing authorisation holders on how to avoid the presence of nitrosamine impurities in human medicines. According to EMA there are known cases when the nitrosamines were leaching to the medicine from the primary packaging therefore the risk assessment and investigation of the packaging is also part of the above mentioned regulation (European Medicines Agency).

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

With the growing number of allergic reactions to the proteins present in Natural Rubber Latex (NRL), the challenge in the medical packaging industry has now become eliminating the possibility of the packaging material as the cause of these allergic reactions. For this reason EC advises pharmaceutical and medical device manufacturers to avoid those components in their products, this is also applicable to packaging materials and labeling materials.

Animal origin (TSE)

Pharmaceutical products having raw materials derived from the animal source have a risk of Transmissible Spongiform Encephalopathy (TSE). This disease can transmit in humans through pharmaceutical dosage forms from cattle infected with the Bovine Spongiform Encephalopathy (BSE) (Pharmaceutical Guidelines). This is not always relevant for labeling materials as they are processed in accordance with European Regulation 1069/2009 and 450/2011 and are therefore not considered a risk for Bovine Spongiform Encephalopathy (BSE) and Transmissible Spongiform Encephalopathy (TSE) however, it is important to inform the customer about the status of the product.

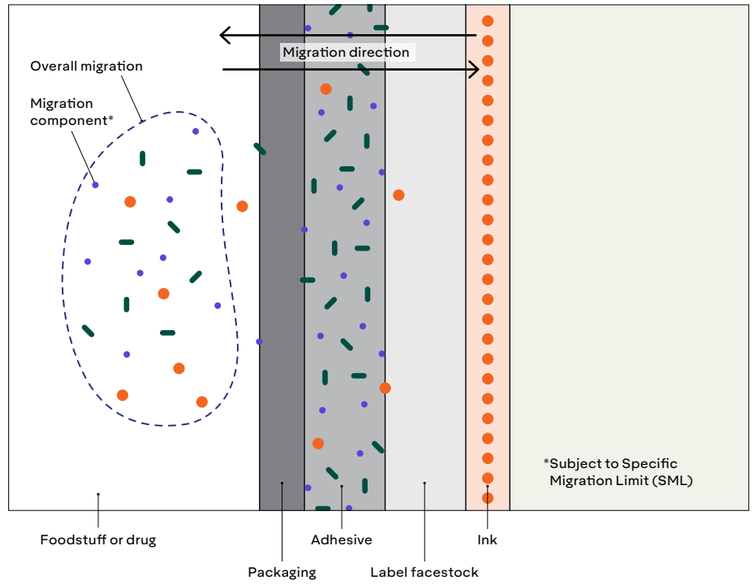
Plastic containers

1935/2004/EC

Although the 1935/2004/EC regulation sets out the general principles of safety and inertness for all Food Contact Materials (FCMs) parts of it are also applicable for the pharmaceutical products. In addition to the general legislation there are certain legislations on specific materials like the EU 10/2011 so called *plastic regulation* is an important mechanism to ensure the safety of plastic materials is the use of migration limits. These limits specify the maximum amount of substances allowed to migrate to food. For the substances on the Union list the Regulation sets out 'Specific Migration Limits' (SML). These are established by EFSA on the basis of toxicity data of each specific substance. To ensure the overall quality of the plastic, the overall migration to a food of all substances together may not exceed the Overall Migration Limit (OML) of **60mg/kg** food (European Commission).

This legislation is important for labeling materials that will be applied on plastic containers like eye drops, pill bottles or plastic syringes. In order to access the migration limit extraction studies are conducted where the label is treated with so called simulants afterwards the migration of adhesive / facestock components is measured.

Applicable for the following applications:
All plastic containers used for medicines, blood and blood components



FDA 175.105

Food and Drug Administration is the US federal agency responsible for protecting the public health by ensuring the safety, efficacy, and security of human and animal medicines, biologic products and food. Code of federal regulations 21 includers the 175.105 section which is concerning “indirect food additives:adhesives” which includes a list of specific chemical substances that are allowed to be used in adhesives if there is no functional barrier between the medicine and adhesive. Plastic is not considered as a barrier therefore, the label materials intended to be used together with the plastic packaging must comply with FDA 175.105 regulation.

Medical devices

ISO 10993 - part 5 and 17

ISO 10993 set entails a series of standards for evaluating the biocompatibility of medical devices to manage biological risk. The aim of ISO 10993 is the protection of humans from potential biological risks arising from the use of medical devices by implementation of appropriate testing methods, risk assessment and management procedures (ISO). With regards to packaging and labels **ISO 10993 part 5** is the most relevant and deals with medical device toxicity. Cytotoxicity is an in vitro test to determine whether the medical device will cause any cell death due to leaching of toxic substances or from direct contact. For packaging and the labeling materials it is critical that no relevant genotoxicity effect is observed meaning that those materials will not have a negative impact on human cells.

Relevant for:
Medical devices: injectors, blood bags, syringes

ISO 10993 Part 17 is dealing with Establishment of allowable limits for leachable substances. Leachables are chemical species that make their way into the product under normal product, application or storage conditions (Thermo Fisher Scientific).

Blood collection containers

ISO 3826-1

ISO 3826 standard concerns a specific type of packaging and products. Plastics collapsible containers for human blood and blood components, blood processing and transportation. In respect to labeling this standard mainly concerns blood bags that require specialised label materials that can not only withstand the rigorous life cycles of blood and plasma bags, but also communicate critical information about origins and content. In order to ensure the highest levels of accuracy, safety, and efficiency for donors and patients worldwide labels must comply with food regulations, and the requirements of ISO 3826 labels need to be tested with regards to the migration of the adhesive through blood bag container material.

Standards and regulations applicable for label and packaging solutions for blood bags:
- ISO 3826 certification on migration behaviour for blood bags
- 10993-5
- FDA 175.105 indirect additives, adhesives and components of coatings

Prescription medicines

Falsified Medicine Directive 2011/62/EU

The “EU Directive on Falsified Medicines” (Directive 2011/62/EU) came into force in February 2019. It reflects an increasingly complex distribution network for medicinal products, with many different players – and a pressing need to ensure reliability across the entire supply chain. European directive EU 2011/62 for medicinal products mandates a number of requirements, and Article 54a relates to safety features in packaging. The article specifies that all prescription medicines must be equipped with a anti-tampering device to verify whether the outer packaging has been tampered with. This can be insured by placing a security seal on the product in the form of a self-adhesive label.

Guidelines on functional packaging for hanging devices

Several ISO norms have been set to ensure that transfusion and infusion bottles stay firmly in place during the administration of liquid pharmaceutical products.

In particular for hanging devices, international standards ISO 15137, ISO 15010 and DIN 58369 describe requirements and test methods for self-adhesive hanging devices (SAHDs). Finished labels need to comply with several requirements such as label attachment, load and water resistance.

In this case, there is no legislation and there are no standard certifications available, but each labeling solution requires its own customised testing. Avery Dennison supports the development process closely, helping converters to evaluate finished labels. We conduct individual assessments following test standard protocols for self-adhesive hanging devices (SAHD) based on ISO and DIN conditions.

Bringing it all together

With the complexity and variety of applicable compliance requirements it is important to have a business partner with expertise and capabilities to manage it. At Avery Dennison we have a dedicated team of experts who are overseeing all aspects of applicable compliance and making sure that our products fulfill those requirements additionally as a part of our extended service on our pharmaceutical adhesives we offer change management and risk assessment service.

Whenever a change is made in a pharmaceutical product, its impact on performance must be assessed, a complete change management documentation file has to be created, and the results must be communicated to pharmaceutical manufacturers and third parties. Avery Dennison offers advanced notification of product changes, and provides pharmaceutical customers with the business-friendly support needed to manage pharma materials during their entire production lifetime:

Guaranteed availability of pharma adhesives

- 1 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
- Customised test reports
- Change notification statement / risk assessment
- Technical storyline and validation report

Testing Services
With more than 80 years of experience in the self adhesive materials industry we are well aware that every application is unique. Our regional technical sales specialists are available for you to assist in choosing the best material for your application. For more advanced and customised material selection / qualification we offer testing services in our European R&D center in Leiden, Netherlands. In the state-of-the-art facility we are offering a variety of test methods and protocols suited specifically to the needs of the pharmaceutical industry such as mandrel (small diameter) performance, high speed dispensing, sterilization resistance, and print durability to name just a few.

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 labelling. Contact your business development manager today to find out how Avery Dennison Pharmaceutical Labelling Solutions can meet and exceed your needs.

Avery Dennison Corporate (NYSE: AVY) is a global materials science manufacturing company specializing in the design and manufacture of a wide variety of labeling and functional materials. The company's products, which are used in nearly every major industry, include pressure-sensitive materials for labels and graphic applications; tapes and other bonding solutions for industrial, medical, and retail applications; tags, labels, and embellishments for apparel; and radio frequency identification (RFID) solutions serving retail apparel and other markets. Headquartered in Glendale, California, the company employs approximately 30,000 employees in more than 50 countries. Reported sales in 2018 were $7.2 billion.

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