Label Qualification

Key Considerations and Resources to Guide Successful Qualification

AN ADEPT GROUP WHITE PAPER

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Qualification Considerations and Planning for Labels

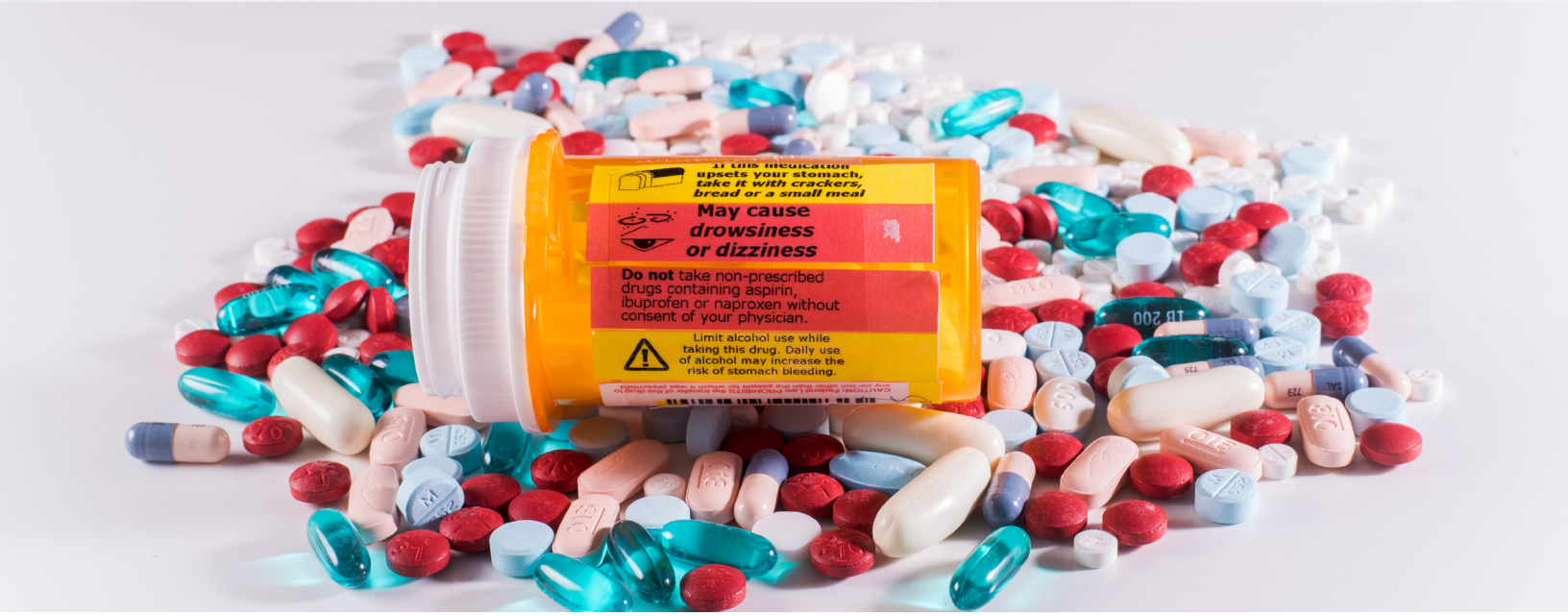
Labeling is an integral part of the manufacture and sales of drugs and medical devices. The label provides product identification, instructions for use and safety information. Missing labels or illegible print can result in misbranded product, which may result in patient safety risks, product recalls and ultimately, damage to brand reputation.

In order to avoid these risks, executing a well-planned label material and print qualification will ensure that your product labeling remains intact during distribution, storage and dispensing. This paper focuses on qualification considerations and planning for labels with permanent pressure-sensitive adhesive.

Label Requirements

While labeling requirements for drugs and medical devices are similar, there are some differences, especially within the recent Serialization and UDI regulations.

Most of these labeling requirements are specified in the Code of Federal Regulations (CFR), but others come from industry standards and specific industry agreements within the supply chains of the pharmaceutical and medical devices industries. Beyond the CFR labeling guidance provided by the FDA, the pharmaceutical industry follows GS1 standards and additional guidance provided by the Healthcare Distribution Alliance (HDA). The medical device industry uses GS1 standards as well, but also incorporates standards set forth by the International Organization for Standardization (ISO). Additionally, there may be a variety of differences in regulations for products intended for distribution and use in countries outside the U.S.



Some requirements, such as the inclusion of a lot code, expiration date, product name, product code, NDC number and barcode, are common across industries and markets. Still, there can be subtle differences in requirements for print format, location and the required content of the text on the label. Requirements may also vary as they pertain to inclusion of manufacture date or the format of expiration dates.

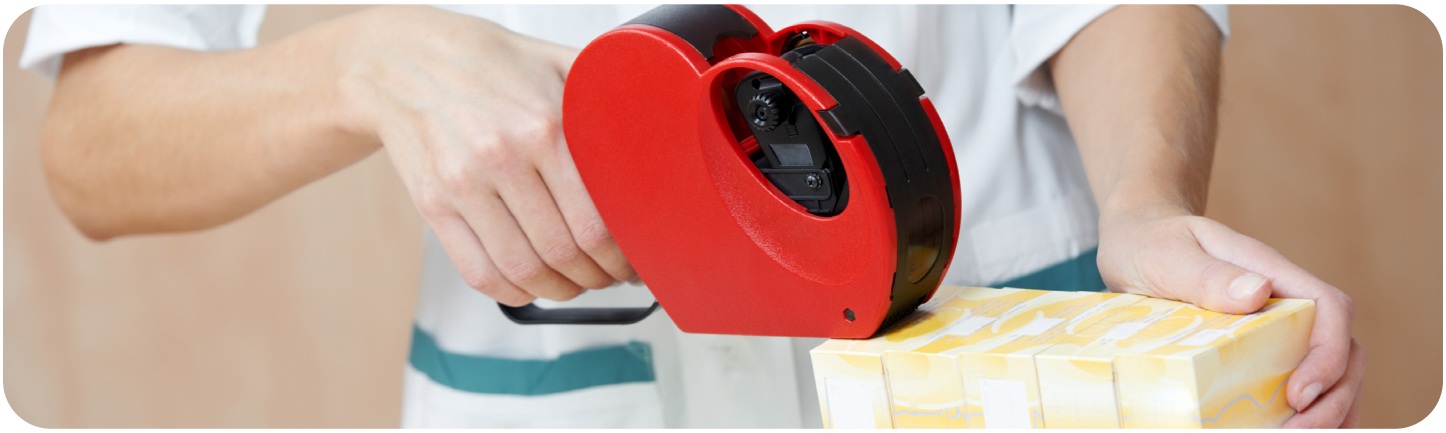
For example, the pharmaceutical industry in the U.S. mainly adheres to the MMM YYYY alphanumerical format, e.g. DEC 2025, for its expiration dates. U.S. medical device manufacturers tend to apply ISO's standard numeric MM YYYY format, e.g. 12 2025, for expiration dates.

Label Requirements Cont.

Bar code requirements and the creation of the content linked to them present a unique set of their own challenges. Pharmaceutical manufacturers must apply the FDA's Drug Supply Chain Security Act (DSCSA) rules, while medical device manufacturers must adhere to the FDA's Unique Device Identification (UDI) system. Naming conventions for bar code content differ significantly between pharmaceutical products and medical devices. Pharma brands include Global Trade Identification Number (GTIN), Serial Shipping Container Code (SSCC) and serial number in their bar codes, whereas bar codes on medical device labels must include UDI-DI and UDI-PI attributes along with the serial number for the product. Pharma brands must convert their NDC number into a GTIN when applying a bar code, while medical device brands must convert their UPC code into a GTIN.

For shipping labels, manufacturers of pharmaceutical products generally apply Healthcare Distribution Alliance (HDA) rules, while most medical device manufacturers adhere to standards issued by ISO. There are also Labeler Codes that identify the organization that prints and applies the labels to the product; in most cases, this is the manufacturer. The pharmaceutical industry typically relies on GS1 for their Labeler Codes and registration, while medical device manufacturers get their Labeler Codes and registration from the Health Industry Business Communications Council (HIBCC).

For packaging professionals in life science industries, the mix of regulations, industry standards and best practices that apply to labeling can be confusing. While this is doubly true for those whose work touches both pharmaceuticals and medical devices, it is important for everyone in those industries to understand the complex interaction of these regulations and standards to complete a successful label qualification and ensure regulatory compliance. There is no consolidated resource or central repository for these rules, so a packaging team's best asset is a labeling expert with experience navigating the complex landscape.



Label Qualification Planning

When planning a labeling qualification, it's important to consider the product labeling materials, the label printing and application processes, and distribution conditions that can affect label performance. Performing a risk assessment will help to identify high-priority risks to concentrate on, along with a means of mitigation that can be addressed in qualification testing. Label materials and processes used in the qualification must be controlled. The measurement systems used must have minimal variation and be capable of consistently classifying acceptable and unacceptable samples that are inspected. Be sure to take these considerations into account:

Test Sample Compliance

Prior to executing testing, confirm that the label material used has been certified as compliant with the specification requirements.

Label Printing

One label may contain print generated by different types of printing methods. Each printing process used must be evaluated, as each type of print may perform differently under test conditions.

Variable information such as lot code, expiration date and serial number or UDI may be printed in-house on a label, carton or shipping container during the packaging process. Laser printing, thermal transfer or ink jet technologies are typically used to print variable information.

In-house printing processes must be qualified before starting a label qualification. The qualified printing process settings (or the minimum/maximum operating range if a process range is specified) must be capable of generating consistent, legible print and barcodes meeting ISO/IEC quality standards. In-house printing process settings used to print samples for testing are documented in the qualification protocol.

Fixed information and high-quality color graphics are typically preprinted by label suppliers. Suppliers have the equipment and expertise to print on a variety of label materials and apply a protective coating over the printing that is highly resistant to print abrasion.

TYPES OF PRINTING IN PACKAGING

- Inkjet Printing (continuous or cartridge)
- Laser edging
- Labeling with pre-printed labels (e.g. digital printing)
- Labeling with thermal transfer printed labels

TYPES OF PRINTING PROCESSES

- Lithography
- Flexography
- Digital
- Rotogravure
- Silkscreen

Label Qualification Planning Cont.

Label Materials and Adhesives

The same label material may be applied to multiple surfaces on a product or package. Adhesives can perform differently on each surface. Qualification samples should evaluate label samples applied to all of the surfaces intended to be labeled. Labels applied to a curved surface such as a bottle have a greater challenge for adhesion, so it's important to use representative samples that will confirm suitability of the label adhesive for this type of application.

Manufacturing Processes

In addition to standardizing label materials and adhesives, it's equally important to standardize manufacturing process testing. Qualification samples should be prepared using the actual process for label application – manual or automatic. Manually applied labels can introduce a high level of variation in both application pressure and label adhesion. If the packaging line utilizes a number of operators to manually apply labels, consider using more than one operator to prepare qualification samples and introduce as much application variation into the process as possible. Samples produced using an automatic label applicator should utilize the label applicator qualified process settings.

For sterilized products, include samples exposed to the maximum number of sterilization cycles or dosage allowed in the manufacturing process.

Label Qualification Planning Cont.

Inspection Considerations

Inspection methods with measurable inspection criteria are established and documented in the qualification protocol.

Uncontrolled lighting conditions and inspection distance can produce variation in visual inspection results. Conditions for visual inspection should be defined to minimize variation. For example, ASTM D4267 defines the conditions for visual inspection of parenteral drug labels.

ANSI MH10.8.13 contains standards for label performance tests, including recommendations for quantifiable inspection criteria. Controlling the inspection process by providing consistent inspection conditions, defining clear, measurable accept/reject criteria, and training inspectors reduces inspection subjectivity. Here are some guidelines for establishing visual inspection criteria:

- Quantify the number and size of visual defects caused by loss of label adhesion, such as lifted edges, the size and number of bubbles under the label, and wrinkles in the label material. Label surface defects affecting print legibility or securement of the label are unacceptable.
- Clearly identify the characteristics for illegible and legible print. Illegible print may include missing letters or numbers, or extreme label or print discoloration. Broken letters or smeared print may be legible if the characters can still be identified.
- Control samples can be used as a before/after testing comparison to confirm whether physical changes to labels have occurred.
- Define visual acceptance criteria for label discoloration, adhesive bleed at the label edges, material delamination and surface abrasion.
- Check the label material specification provided by the supplier for a minimum/ maximum range for adhesive peel strength. A reduction in peel strength during an aging study may still be within acceptable limits.
- Bar code print quality grades can be measured using a bar code verifier. ISO/IEC 15426-1 and 15426-2 contain specifications for linear and 2D bar code grades. Establish a minimum acceptable quality grade for pre-test qualification samples along with a minimum grade for acceptance after testing.
- Bar code content compliance with GS1 standards must be assured for all printed 1D or 2D code type prints on packages and shipping units. That must be part of the label qualification.

Label Qualification Planning Cont.

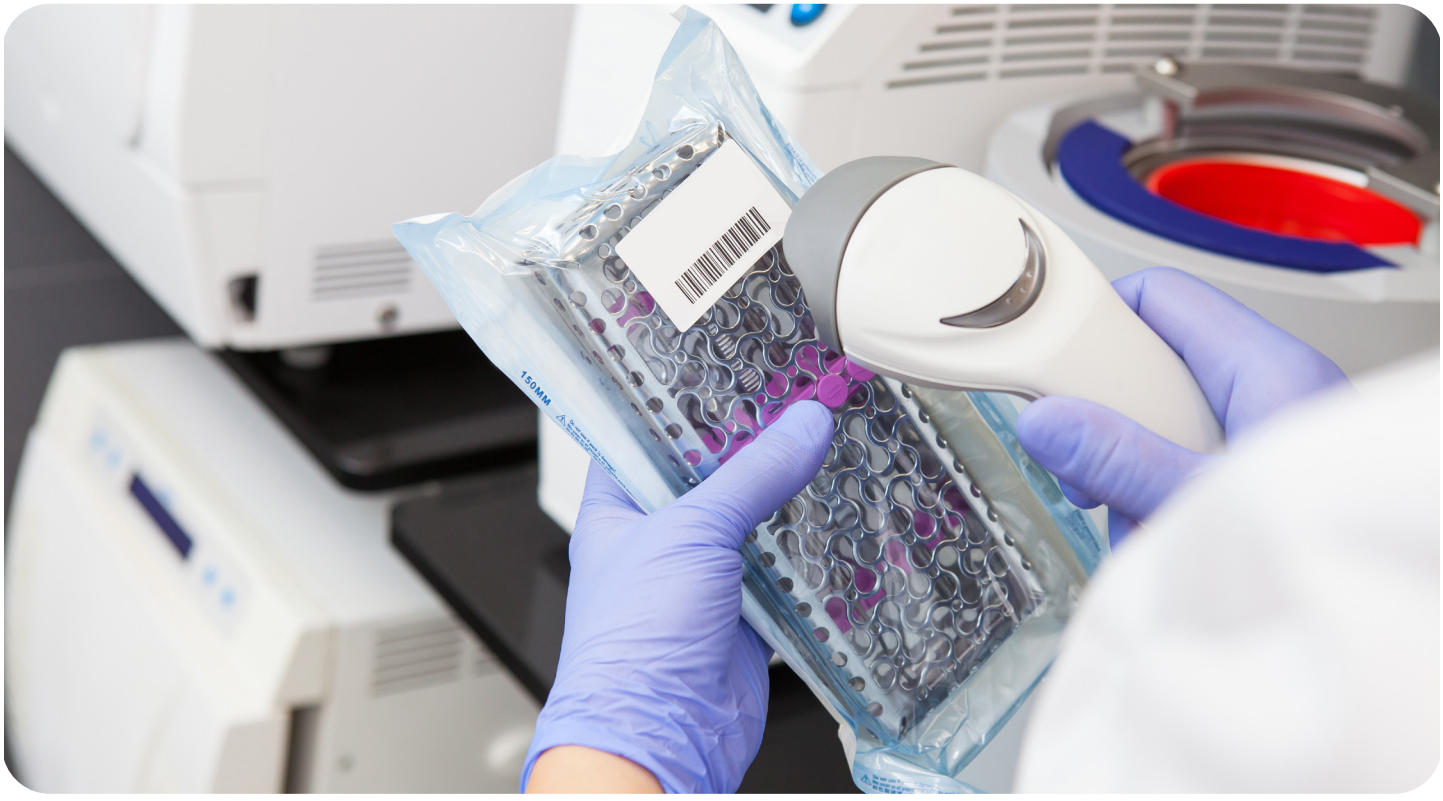
GS1 Compliance

Updated bar code regulations stipulate that all printed 1D and 2D codes must comply with ISO and GS1 standards to facilitate readability and decoding at each scan point throughout the supply chain, up to and including the point of sale. The GS1 standard applies to all industries using UPC bar codes, UDI bar codes or product identification barcodes with multiple data elements. Adherence to GS1 standards is required for GxP compliant qualification and validation.

Label Lifecycle

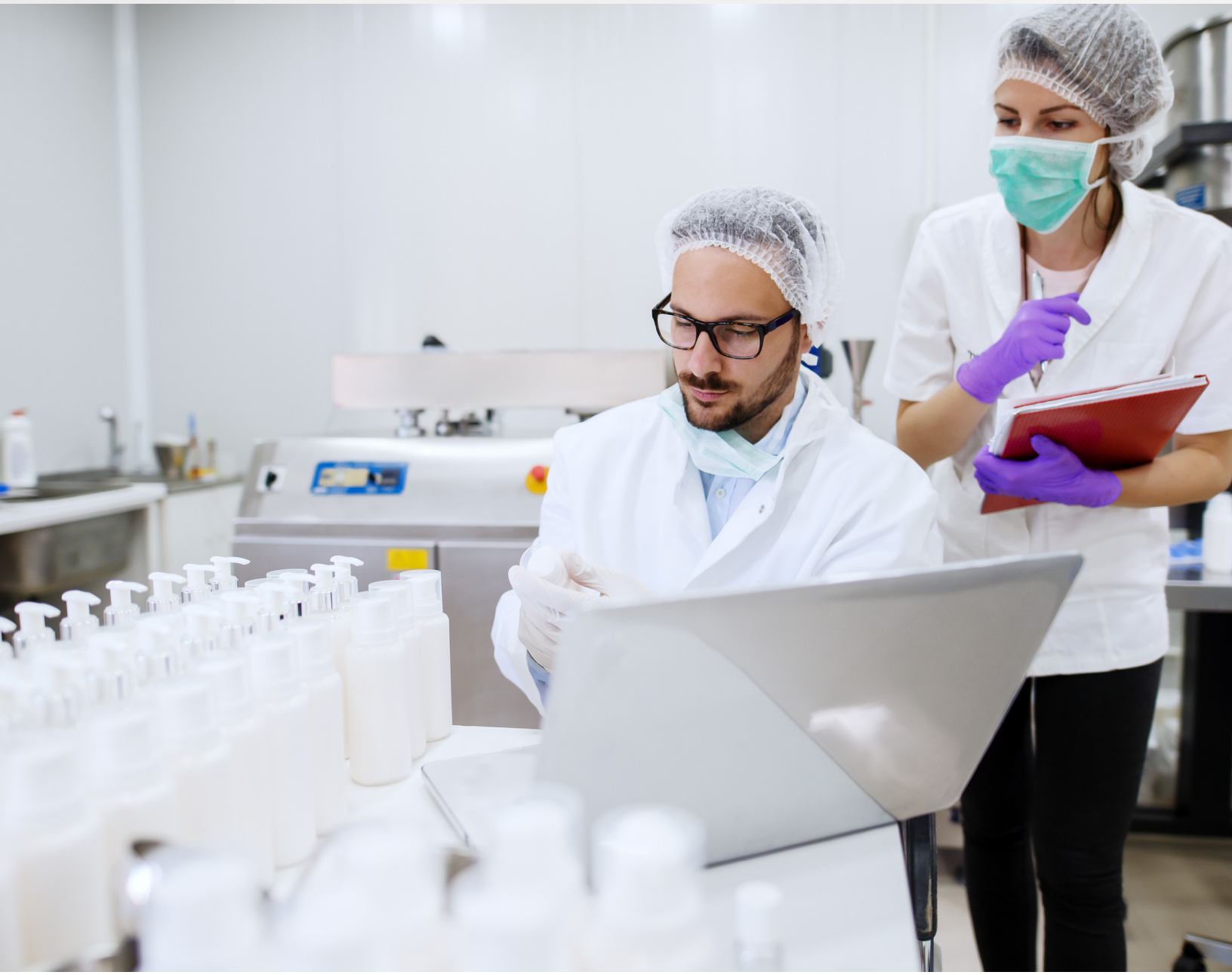
Outer package prints, secondary and tertiary labels must retain their quality and compliance throughout the supply chain and the lifecycle of the product. Temperature changes, weather, sunlight and transportation must not degrade the label or print before the product's expiration date.

Packages, cases, shippers and pallets that feature thermal transfer labels must undergo rigorous testing to ensure they will remain compliant and readable throughout the package's lifecycle. This can be challenging for products with a long lifespan, meaning thermal transfer labels may not be the best option for medical device packaging.



Testing Execution

Testing should represent the conditions that the labeling will be exposed to during the manufacturing process, storage, distribution, and dispensing of packaged products at the healthcare provider.



Distribution, Storage and Handling Simulations

A qualification must evaluate the effects on label adhesion and print legibility due to exposure to distribution and handling conditions, including temperature exposure, shock and vibration.

Environmental simulations should be representative of expected temperature and humidity exposure, including extremes. Freeze/thaw processes representative of conditions found during drug manufacturing and dispensing should be included in the simulation if they can occur.

Exposure to simulated distribution conditions will confirm that label quality is not affected in transit. Surfaces of materials such as corrugated fiberboard are abrasive and can damage labels packed in shipping containers that are exposed to vibration conditions. Exposure to shock and vibration can also cause label tearing, wrinkling or other damage.

Accelerated aging and real-time studies simulate storage throughout the shelf life of the product to determine if degradation of the label material, adhesive or print will occur over time. The possibility of label adhesive or ink migration over time from a label applied to a primary drug container should be evaluated if a potential risk exists.

An understanding of the process used for manufacturing and dispensing of a drug or device will determine if the package surface may be exposed to solvents or other chemicals. Smeared or missing print, destruction of the label surface, or removal of the label adhesive could occur. Isopropyl Alcohol, other antiseptics and surface disinfectants can come in contact with the labeling if the package is wiped down or opened by a healthcare practitioner handling an antiseptic as part of product dispensing. A test simulating the dispensing or processing conditions can confirm whether the printed labels are chemical resistant.

Label Testing Information Resources and Standards

Label testing and bar code quality standards are available from various organizations. The following section lists testing and standards published by various organizations that are useful resources for a label qualification.

ANSI MH10.8.13	Performance Requirements and Test Procedures for Labels Incorporating Linear Bar Code and Two-Dimensional (2D) Symbols – Part 1: Pressure-Sensitive Labels
PRESSURE SENSITIVE TAPE COUNCIL	Test Methods for Pressure Sensitive Adhesive Tapes
(WORLD-WIDE ASSOCIATION FOR SELF-ADHESIVE LABELS AND RELATED PRODUCTS)	FINAT Technical Handbook Test Methods
ASTM F1319	Standard Test Method for Determination of Abrasion and Smudge Resistance of Images Produced from Business Copy Products (Crockmeter Method)
ASTM F1478	Standard Test Method for Determination of Abrasion Resistance of Images Produced from Copiers and Printers (Taber Method)
ASTM F1980	Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices
ASTM F2250	Standard Practice for Evaluation of Chemical Resistance of Printed Inks and Coatings on Flexible Packaging Materials
ASTM D4267	Standard Specification for Labels for Small-Volume (100mL or Less) Parenteral Drug Containers

Label Testing Information Resources and Standards Cont.

ASTM D4332	Standard Practice for Conditioning Containers, Packages, or Packaging Components for Testing
ASTM D5264	Standard Practice for Abrasion Resistance of Printed Materials by the Sutherland Rub Tester
ASTM D6252	Standard Test Method for Peel Adhesion of Pressure-Sensitive Label Stocks at a 90° Angle
ASTM D7932	Standard Specification for Printed, Pressure-Sensitive Adhesive Labels for Use in Extreme Distribution Environments
ASTM F1478	Standard Test Method for Determination of Abrasion Resistance of Images Produced from Copiers and Printers (Taber Method)
21 CFR PART 801	Labeling
21 CFR PART 820, SUBPART K	Customary Conditions of Processing, Storage, Handling, Distribution, and Where Appropriate, Use
21 CFR SUBPART A AND B, SECTION 201	General Labeling Provisions, defines the labeling and barcoding requirements for pharmaceuticals
ISO/IEC 15415	Information Technology – Automatic Identification and Data Capture Techniques – Bar Code Print Quality Test Specification – Two Dimensional Symbols

Label Testing Information Resources and Standards Cont.

ISO/IEC 15416	Bar Code Print Quality Test Specification – Linear Symbols Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics, Chemistry, Manufacturing and Controls Documentation, U.S Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 1999
ISO/IEC TR 29158	Quality parameters and grading process for DPM codes, similar to ISO 15415, with a few key differences. AIM DPM calculates the global threshold, using a more sophisticated algorithm than ISO 15415, which allows the use of 30-, 45-, 90-degree, and dome lighting.
ISO 22742	Guidance for product packaging with labels containing a linear bar code and two-dimensional symbols
ISO 15394	Packaging — Bar code and two-dimensional symbols for shipping, transport and receiving labels
GS1 GENERAL SPECIFICATIONS	The foundational GS1 standard that defines how identification keys, data attributes and barcodes must be used in business applications.
GS1 HEALTHCARE GTIN ALLOCATION RULES	GTIN Allocation Rules for the Healthcare Sector, which apply to the pharmaceutical and the medical device industries
GS1 US HEALTHCARE	Guidance for Pharmaceutical Products Marked with Both UPC-A and GS1 DataMatrix
GS1 US STANDARDS GUIDANCE FOR ASSIGNING DIS USING GLOBAL TRADE ITEM NUMBERS (GTINS)	Based on the GS1 US Using the GS1 System for U.S. FDA UDI Requirements Implementation Guideline

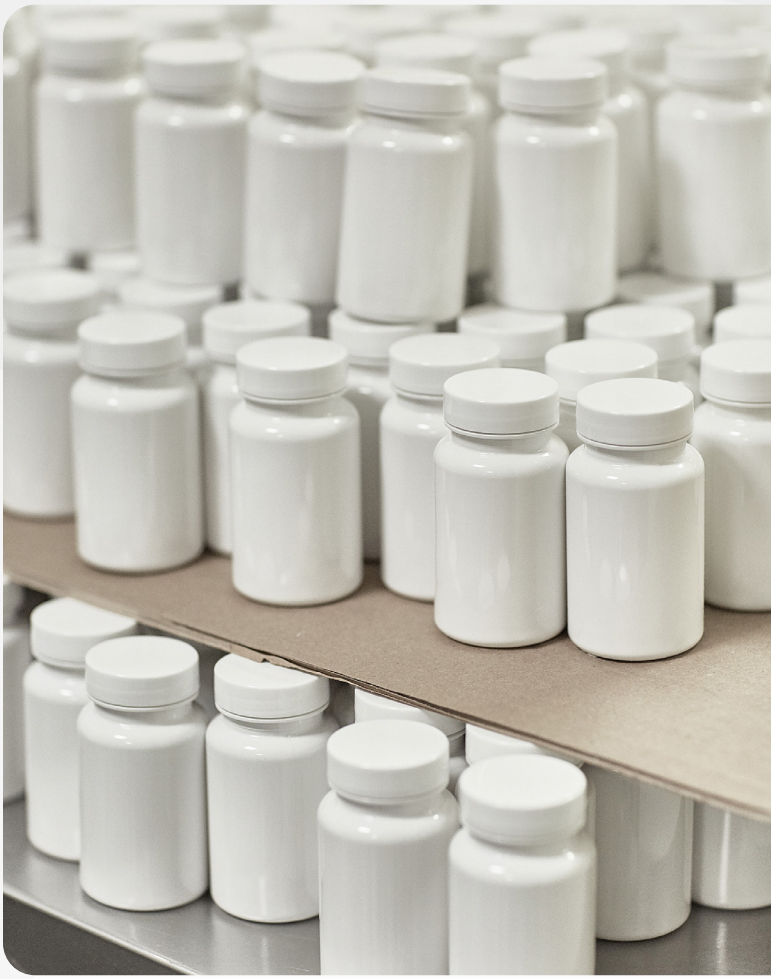
Label Testing Information Resources and Standards Cont.

GS1 HEALTHCARE US IMPLEMENTATION GUIDELINE	Applying GS1 Standards to U.S. Pharmaceutical Supply Chain Business Processes
ISO 17351	Packaging – Braille on packaging for medicinal products
ISO/IEC 15417	Specification for linear 1D barcodes in Code 128 format for numeric and alphanumeric content
ISO/IEC 15434	Syntax for automatic identification and data capture techniques commonly used in 2D barcodes, such as Data Matrix
ISO/IEC 16022	Data Matrix bar code symbology specification
ISO/IEC 15424	Data Carrier Identifiers, including Symbology Identifiers, IDs for distinguishing different barcode types
ISO/IEC 15459	Unique identifiers - specifies a unique string of characters for the identification of individual transport units

Contact Us

Partner with Adept

Like many aspects of business for Life Sciences brands, labeling is governed by complex regulations and getting it wrong could have serious consumer safety implications. The team at Adept Group has a wealth of experience in helping pharmaceutical and medical device brands successfully navigate the label qualification process. Whether you need a single consultant to help with labeling for a new product or a full team of engineers to lead a major packaging overhaul, we have a deep bench of experts ready to help you design, qualify and implement your next project successfully, get in touch.



Resources:

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https://www.gs1us.org
https://www.iso.org
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