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ENGINEERING PACKAGING EXCELLENCE

Considerations for Successful Label Qualification

Compliant Labeling for the Pharmaceutical and Medical Device Industries

An Adept Packaging White Paper

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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

Labeling requirements for drugs and medical devices are specified in the Code of Federal Regulations.

> *"Labels shall be printed and applied so as to remain legible and affixed during the customary conditions of processing, storage, handling, distribution, and where appropriate, use."* (CFR 21, Part 820, Subpart K)

CFR 21, Subpart A and B, Section 201, General Labeling Provisions, defines the labeling and bar-coding requirements for pharmaceuticals. §201.56 contains specific requirements on the content and format of labeling for human prescription drug and biological products. Examples of some of the labeling requirements for prescription drugs included in CFR 21, Subpart A and B, Section 201 are listed here.

> *"A drug or drug product (as defined in §320.1 of this chapter) in finished package form is misbranded under section 502 (a) and (b)(1) of the act if its label does not bear conspicuously the name and place of business of the manufacturer, packer, or distributor."*

> *"When an expiration date of a drug is required, e.g., expiration dating of drug products required by §211.137 of this chapter, it shall appear on the immediate container and also the outer package, if*

any, unless it is easily legible through such outer package."

"The lot number on the label of a drug should be capable of yielding the complete manufacturing history of the package. An incorrect lot number may be regarded as causing the article to be misbranded."

"Each drug product described in paragraph (b) of this section must have a bar code that contains, at a minimum, the appropriate National Drug Code (NDC) number in a linear bar code that meets European Article Number/Uniform Code Council (EAN/UCC) or Health Industry Business Communications Council (HIBCC) standards or another standard or format that has been approved by the relevant Food and Drug Administration Center Director. Additionally, the bar code must:

Be surrounded by sufficient blank space so that the bar code can be scanned correctly; and remain intact under normal conditions of use."

There are numerous complex regulations surrounding drug and medical device labeling, which need to be understood and successfully qualified to ensure regulatory compliance.

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.

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.

Inspection Considerations

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

Types of Printing Processes

- Lithography
- Flexography
- Digital
- Rotogravure
- Silkscreen

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 as follows:

> *"Copy legibility shall be measured in a light of 215 lx (lux) 20 fc (foot candles) at a distance of 500 mm (19.7 in.) by a person with 20/30 unaided or corrected vision. A contrasting background may be used."*

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.

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 fibreboard 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
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
ISO/IEC 15415	Information Technology – Automatic Identification and Data Capture Techniques – Bar Code Print Quality Test Specification – Two Dimensional Symbols
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

Partnering 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 Packaging 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.

Resources

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=820&showFR=1&subpartNode=21:8.0.1.1.12.11

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=201&showFR=1&subpartNode=21:4.0.1.1.2.1

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.56

https://www.ansi.org/