Quality System Regulation Labeling Requirements

Introduction
Medical device manufacturers must incorporate in their quality assurance (QA) program several elements that relate to labeling in order to meet the Good Manufacturing Practice (GMP) requirements of the Quality System regulation. The QA program must be adequate to ensure that labeling meets the GMP device master record requirements with respect to legibility, adhesion, etc., and ensure that labeling operations are controlled so that correct labeling is always issued and used.

Labeling includes equipment labels, control labels, package labels, directions for use, maintenance manuals, etc. The displays on CRT's and other electronic message panels are considered labeling if instructions, prompts, cautions, and parameter identification information are given.

Various sections of the QS regulation have an impact on labeling: Section 21 CFR 820.80 requires the inspection and testing of incoming materials including labeling; and 21 CFR 820.70 requires buildings to be of suitable design and have sufficient space for packaging and labeling operations. 21 CFR 820.120 deals with specific requirements for the control of labeling. It applies to the application of labeling to ensure legibility under normal conditions of use over the expected life of the device; and also applies to inspection, handling, storage, and distribution of labeling. FDA considers a device to be adulterated if these requirements are not met. These requirements do not apply to the adequacy of labeling content, except to make sure the content meets labeling specifications contained in the device master record. However, failure to comply with GMP requirements, such as proofreading and change control, could result in labeling content errors. In such cases, the device is misbranded and adulterated.

Specifications are required in the design history file (DHF) 21 CFR 820.30 for the content and physical design parameters of labels. Labeling specifications are: engineering drawing and/or artwork for each label, appropriate inspection or control procedures, and appropriate procedures for attaching the labels. All procedures, drawings, and artwork must have the name of the preparer, an approval signature, and a date. The approval signature, date, etc., may be on the backside of artwork or on a label approval form. Further, artwork may contain only an identification code or title if the "content" of the artwork is duplicated on approved engineering drawings or adequately identified (cross-referenced) with respect to the label approval form.

Hard copy labels, package inserts, and similar labeling are specified and purchased as components. For correct purchase and use of labeling, specifications are usually stated on engineering drawings and/or purchase specifications. Thus, artwork or "copy" alone will not fulfill the device master record requirements for labeling except for the most simplistic labeling such as brief errata sheets.

The engineering drawings or purchase specifications and mounting procedure must specify, as appropriate, the label substrate, dimensions, ink, finish, mounting method, etc., so that the purchased label will remain attached and legible during the customary conditions of processing, storage, handling, distribution, and use.

Front panels, other instrument panels, meters, fuses, pushbuttons, and the like often are labels or contain labels and must, as appropriate, meet device master record and control requirements. Component specifications, assembly drawings, and test/inspection procedures may be appropriate controls to prevent mixup of meters, pushbuttons, and other labeled instrument controls. Controls to prevent mixups are generally not needed for front and other instrument panels.

Whether a firm considers a software driven display to be labeling or data makes little difference under the Quality System regulation, because either way, the finished device labeling or data must meet the device master record specifications. When firms develop and validate software, they should also review these electronic displays to see that the "labeling" meets all applicable requirements, such as adherence to specifications in the device master record, correct parameter identification, agreement with the instruction manual, and of course, correct display of performance data.

When reviewing or auditing labeling operations, it is wise to keep in mind that the Quality System regulation contains flexible requirements and thus allows flexibility in a quality assurance program. The degree of labeling control needed to satisfy the Quality System regulation varies considerably for different devices and operations. In order to avoid wasting money and increasing the cost of health care, manufacturers need to give considerable and prudent thought to the appropriate level of control needed for their operations. Information and guidelines presented in this chapter should aid manufacturers in making these decisions. The level of control needed should be reconsidered when products are added or changed. Likewise, the controls needed and success of the existing control program must be reviewed during QA system audits.

Specific Requirements for Labeling
Label Integrity
All labels must be designed and applied to devices and containers so that the labels will remain in place and legible during the customary conditions of distribution, storage, and use. Likewise, other labeling, such as user instructions, should remain legible during customary storage and use. For example, labeling printed by machines onto plastic in vitro diagnostic media plates is sometimes smeared and thus is inadequate [FD&C 502(f)]. The manufacturers of such devices must assure that the print is legible and will remain legible until used.

Receipt and Inspection
Upon receipt, all packaging and labeling materials, including preprinted containers, inserts, and preprinted packaging materials must be examined and, acceptance activities performed to assure conformance with specifications. Also, samples of labels must be proofread by a designated individual(s). After being accepted by a responsible individual, these components may be placed into inventory or into production. These acceptance activities must be recorded in the device history record as required by 21 CFR 820.80(e) and 21 CFR 820.120 to show that inspection and proofreading were performed. The acceptance record for device labeling should be kept simple.

Area Separation and Inspection
All labeling and packaging operations should be separated to the degree necessary to make certain there are no mixups between similar products or labels. Separation may be either a physical or spatial separation or by performing the labeling and packaging at different times for different devices. Separation is not required when mixups are impossible such as the case of labels from panels that fit the intended family or instruments (devices).

The likelihood of a labeling mixup determines how stringent production area controls should be. For example, label control need not be stringent if only dissimilar products and labeling are processed. Before beginning any packaging and labeling operation in which mixup could occur, the production area and equipment for the operation must be thoroughly examined to make certain that any devices and labeling materials remaining from previous operations have been removed. It is important to make certain that the surrounding area, tables, packaging lines, printing machines, and other equipment are cleared of labels and other materials used in the previous operation.

Unused labeling that contains pre-coded serial numbers, manufacturing date, expiration date, control number, etc., should be destroyed and not returned to the label storage area. The Quality System regulation does not require reconciliation of the number of labels used versus the number issued, although this control is recommended for some devices, such as when different sizes of the same product are being packaged or otherwise labeled.

Storage
All printed packaging and labeling materials, including preprinted containers, inserts and preprinted packaging materials, must be stored in an area and manner suitable to prevent mixups (21 CFR 820.120). Labeling should be identified and segregated to the degree necessary to prevent mixing of similar labeling. Access to labeling should be limited to authorized personnel.

Storage control should be appropriate for the number and kind of devices. For example, a firm that manufacturers only one product with one label does not need an elaborately controlled storage area. Similarly, a firm with only a few types of devices having dissimilar labeling would not normally require stringent control.

One case that requires dedicated attention to storage and control is prelabeled "sterile" but "not-yet-sterilized" devices. Firms must make certain that mixups cannot occur. Also make certain that all such samples, if used for market promotion, are sterile or stamped with a manifest caution statement because a package and labeled market-promotion sample might be used by the recipient.

Label Check and Record
When issued for use, labeling must be carefully examined to make certain the contents of the labeling comply with the labeling specifications in the device master record for the specific device being produced. This examination must include any control numbers or expiration dates used on the labels. A record of this issuance check, including the date and name of the person performing the examination, must be made in the device history record.

If used, expiration dates must reflect the time after final packaging during which the device is fit for its intended use when stored and used per its labeling. The manufacturer should have stability test data which establishes the interval that the device remains fit for use.

If label mixups cannot occur--for example, a firm makes only one device or uses only one label--and there are no control numbers or expiration dates, the original inspection when the labeling was placed into inventory is an adequate check for compliance with the device master record specifications.

Changes
Labeling is part of the device master record; therefore, all changes to labeling must be made under a formal change control system similar to that required for specifications (21 CFR 820.30(i)). Any changes to labeling must be formally reviewed and authorized before implementation.

When making changes to primary aspects of a device or to primary documentation, the review
group must determine if any secondary items such as labels or instructions are affected and also need changing. There should be a check-off block on change-order forms for recording that the effect of the primary change on labeling was considered and appropriate action was taken.

Relabeling and Over-labeling

Over-labeling by placing a new label over an old label is discouraged by FDA but is acceptable as long as the new label and its use meet GMP requirements for attachment, legibility, reprocessing, and change control. (Over-labeling is also discouraged in some foreign countries.)

Control Number

Devices intended for surgical implant into the body or to support or sustain life and whose failure to perform when properly used in accordance with instructions for use provided in the labeling can be reasonably expected to result in a significant injury to the user require a control number on each unit, lot, or batch of finished devices and where appropriate components for traceability [21 CFR 820.65(7)]. This means a control number for the finished device, and not the label itself. Most labeling, however, also contains another number, such as a drawing number, for control of labeling configuration and procurement.

The control number for traceability need not be on every label on the device; however, the control number must appear on the unit label that goes to the ultimate user. The label on a shipping carton for bulk items does not meet this requirement because bulk items may go to central distribution point in the user-facility and the shipping carton would most likely be discarded. In order to meet this traceability requirement, a label that would most likely reach the nurse or other user station must have the control number.

Sterile Device Labeling

Special attention should be given to the labeling of sterile devices. Devices that are not sterile in their entirety (for example, sterility may be needed only for the lumen of certain devices) must be labeled to properly inform users what is actually intended to be "sterile" in the package. For example, a possible limiting statement might be: "Caution: Only the fluid path of the set is sterile and non pyrogenic. Do not use in a sterile or aseptic area without proper precautions."

Some devices are intended to be sterilized by the user before use. In this situation, the labeling should provide adequate information as to at least one suitable method of sterilization and any precautions or safeguards to be followed. For example, the labeling should describe any:

- special cleaning methods required;
- changes in the physical characteristics of the device that may result from reprocessing which affect its safety, effectiveness, or performance; and
- limit on the number of times resterilization and reuse can be done without affecting the safety or effectiveness of the device.

In the case of single-use sterile devices, some manufacturers include labeling to advise against resterilization and reuse. Some devices are simply not designed or constructed to be relabeled, and may not be capable of withstanding the necessary recleaning and resterilization procedures. Where reuse is common practice, manufacturers are encouraged to provide the information described in the above list.

The label of multi-device kits or packages containing a combination of sterile and nonsterile products must not state or imply that all contents are sterile.

The need for users to have instructions on how to open a sterile device package to avoid contamination of the device also needs to be evaluated, and when necessary, such instructions should be included in the labeling.

When a manufacturer modifies a device, the manufacturer must also review the labeling to make certain that it reflects current revisions and specifications. Some manufacturers identify labeling with a drawing number plus a revision code or date as an aid in identifying current labeling. The package insert or other labeling for in vitro diagnostic products is required to contain the revision date [21 CFR 809.10(9)(b)(15)].

Shelf-life dating solely for package integrity and sterility is not usually required by FDA for general medical devices. There may be a need for expiration dating when a particular component of a device, such as a battery or diagnostic reagent, has a finite useful life. Labeling for in vitro diagnostic devices [21 CFR 809.10(12)(a) and (b)] requires an expiration date or some other means by which users may be assured of quality at the time of use. This requirement applies to both sterile and nonsterile in vitro diagnostic devices.

Although not always required by regulation, most manufacturers of complex devices and sterile devices voluntarily use lot or serial numbers for production control and, if the need arises, to expedite failure investigations, repairs, modifications, or recalls. Lot, batch, or other control numbers are required for:

- certain devices [21 CFR 820.65(12)];
- some products subject to radiological health standards; and
- in vitro diagnostic devices [21 CFR 809.10(13)(a)(9)].

Adequate labeling for a medical device requires proper design and procurement of the labels and
labeling. Design includes labeling content that meets the requirement of the QS regulation as well as the needs of the customer. To achieve these goals a number of concepts must be kept in mind such as: writing to the reader, referring to the actual device in labeling, obvious identification of the controls used, etc.

Contract Sterilization

Finished devices that are terminally sterilized by a firm other than the manufacturer pose a unique labeling problem. A common industry practice is to send the finished device in its final packaging to a contractor for sterilization. The final packaging is labeled as sterile even though the goods are unsterile during shipment from the manufacturer to the contractor. Specific restrictions apply in this instance, and a written agreement between the parties must be in effect [21 CFR 801.150\textsuperscript{14}(e)]. The requirements for the labeling of in process sterile goods in transit to the contract sterilizer are addressed in detail by 21 CFR 801.150\textsuperscript{15}, and covered under Other Labeling Exemptions\textsuperscript{16}. Care must be taken in this situation to eliminate the possibility of an unsterilized product being mistaken for a sterilized product. A firm should seriously consider the use of "visual indicator" labeling to distinguish between product before and after sterilization, e.g., the use of indicator tape with bands that develop color upon exposure to steam or ethylene oxide, or stick-on "dots" which change color upon exposure to radiation. Bear in mind that visual indicators will provide confidence that the product has been exposed to a sterilant and not that the product is sterile. A firm should also consider the use of dosimeters, i.e., a product that undergoes an irreversible change in physical or chemical properties that is proportional to the amount of exposure to a sterilant. Some contract sterilizers affix labeling to a contractor's product in the form of a sterilization number stamped upon the device container, or outer shipping containers. Firms who use the contract sterilizer's lot number as assurance that their devices have undergone sterilization should determine, via an audit of the facility if possible, that sterilization lot numbers are applied after, not before, being subject to sterilization.

Regulations on distribution are contained in 21 CFR 801, Subparts A and E; and Quality Systems Regulation 21 CFR 820.160\textsuperscript{17}. Devices that have been sterilized, held, or shipped to the manufacturer's warehouse or other controlled distribution point before final release must be properly labeled. The pallets, or designated unit, must be marked to indicate the status of the device such as "sterilized: awaiting test results," or an equivalent statement. The company must have undergone sterilization should determine, via an audit of the facility if possible, that sterilization lot numbers are applied after, not before, being subject to sterilization.

Information on other labeling issues\textsuperscript{18}

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