Product Labeling

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- Definitions
- FD&C Act
- Regulations & Requirements
- Types of Labeling
- Labeling Changes
- Additional Info & Guidance Documents

What is a Label?

- Section 201(k) defines 'label' as a:

  'display of written, printed, or graphic matter upon the immediate container of any article…'

What is Labeling?

- Section 201(m) defines 'labeling' as:

  '*all labels and other written, printed, or graphic matter*

  (1) upon any article or any of its containers or wrappers, or

  (2) accompanying such article' at any time while a device is held for sale after shipment or delivery for shipment in interstate commerce.

Misbranding

- Labeling contains false or misleading statements (directly stated or implied)
- Missing required information from label/labeling (CFR, FD&CA, etc.)
- Contains inadequate directions for use including necessary warnings/limitations
- Does not comply with performance standards requirements, if applicable

- Section 201(n) of the Act states that if an article is alleged to be misbranded due to misleading labeling or advertising it needs to be determined if the labeling/advertising is misleading:
  - Based upon the representations that are made or suggested
  - And to what extent it fails to reveal crucial facts or possible consequences resulting from the use based on the representation in the labeling/advertising or under customary or usual use

Labeling Regulations

- Labeling regulations pertaining to medical devices are found in the following Parts of Title 21 of the Code of Federal Regulations (CFR).

General Device Labeling -	21 CFR Part 801
In Vitro Diagnostic Products -	21 CFR Part 809
Investigational Device Exemptions -	21 CFR Part 812
Good Manufacturing Practices -	21 CFR Part 820
General Electronic Products -	21 CFR Part 1010

Labeling for IVD products

21 CFR 809.10

21 CFR 809.10(a) - Product Label

(a) The IVD product label shall state the following:

(1) The proprietary and established name (common)

(2) Intended Use(s)/Indications for Use

(3) Reagent

- Name
- Amount of each reactive ingredient
- Source and activity (biological origin)
- Amount of each reagent

(4) Warnings or precautions statements

- Includes "For In Vitro Diagnostic Use" and any other limiting statements (e.g., For Prescription Use Only")

(5) Reagent – appropriate storage instructions

21 CFR 809.10(a) - Product Label

(6) Reagent – is it still good?
  (i) Expiration date per storage instructions.
  (ii) Visual appearance (e.g., turbidity, color change, etc.)
  (iii) Instructions - simple method how user can determine still acceptable

(7) Reagent - Net contents

(8) Name and place of business of manufacturer, packer, or distributor.

(9) Lot or control number

(10) When information can appear on immediate outer container:
  (i) Immediate container too small
  (ii) Its presence will interfere with the test

21 CFR 809.10(b) – Product Labeling

(b) Accompanying product labeling:

(1) Proprietary and established name (809.10(a)(1)

(2) Intended Use + Procedure type (Qualitative/Quantitative)

(3) Summary and explanation, including:

- Short history of the methodology
- Pertinent references
- Special merits and limitations of the method or product

(4) Principles of the procedure

(5) Reagents (principle & accessory):

- Include 809.10(a)(3) – 809.10(a)(5)*
- Reagent preparation instructions
- Purification procedures or treatment required for use
- Indications of instability or deterioration

*The same or similar information as subsection indicated

21 CFR 809.10(b) - Product Labeling

(6) Instruments (Topics to be included in User's Manual)
- Use or function
- Installation procedures and special requirements
- Principles of operation
- Performance characteristics and specifications
- Operating instructions
- Calibration procedures
- Operational precautions and limitations
- Hazards
- Service and maintenance information

(7) Specimen collection and preparation for analysis
- Special precautions
- Known interfering substances.
- Recommended maintenance of stability of the specimen

21 CFR 809.10(b) - Product Labeling

(8) Procedure: Instructions for Use (specimen receipt to results)
- Calibration – ID and preparation of reference samples/controls
- Use of blanks
- Standard curve, etc. preparation
- Calibration range description (including highest & lowest value)
- Description of QC procedures and materials required
  - Are both positive and negative controls needed?
- State what are considered satisfactory limits of performance

(9) Results (How to calculate or interpret)

(10) Limitation of the Procedure
- List limitations of the procedure
- State known interferents
- If additional follow up testing is necessary

21 CFR 809.10(b) - Product Labeling

11) Expected Values
    - What they are
    - Range in various populations
    - How and in whom the range was established
12) Specific Performance Characteristics
    - Accuracy, precision, specificity, and sensitivity.
    - Summary of analytical & clinical study & data
13) Bibliography
14) 809.10(a)(8)
15) Issue date of the last labeling revision

21 CFR 809.10(c) - Shipping

(c) IVDs are exempt from 809.10(a) and 809.10(b) and from a standard promulgated under part 861 if:

(1) Shipment or delivery for an investigation subject to part 812, if there has been compliance with part 812; or

(2) Not subject to part 812 [see 812.2(c)], if:

(i) In the laboratory research phase of development and not represented as an effective in vitro diagnostic product – all labeling must state prominently: "For Research Use Only. Not for use in diagnostic procedures."

(ii) Being shipped or delivered for product testing before full commercial marketing – all labeling must state prominently: "For Investigational Use Only. The performance characteristics of this product have not been established."

21 CFR 809.10(d)- General Purpose

(d) Labeling of general purpose laboratory reagents and equipment - uses are generally known by persons trained in their use need not bear the directions for use required by 809.10(a) and (b), if:

(1) The label of a reagent shall bear the following information:

- 809.10(a)(1)
- 809.10(a)(3)
- Reagent purity, quality, and amount of impurities present Conformity with recognized & available standard (e.g., ACS, USP, etc.)
- 809.10(a)(4)
- A statement "For Laboratory Use."
- 809.10(a)(5)
- 809.10(a)(7) – 809.10(a)(10)

(2) The label of general purpose laboratory equipment, e.g., a beaker or a pipette, shall bear a statement adequately describing the product, its composition, and physical characteristics if necessary for its proper use.

21 CFR 809.10(e) - ASRs

(e)(1) The labeling for analyte specific reagents (e.g., monoclonal antibodies, DNA probes, viral antigens, ligands) shall bear the following information:

- 809.10(a)(1)
- 809.10(a)(3) - 809.10(a)(9)
- The labeling may also include information on chemical/ molecular composition, nucleic acid sequence, binding affinity, cross-reactivities, and interaction with substances of known clinical significance
- For class I exempt ASRs, statement: "Analyte Specific Reagent. Analytical and performance characteristics are not established"
- For class II and III ASRs, statement: "Analyte Specific Reagent. Except as a component of the approved/cleared test (Name of approved/cleared test), analytical and performance characteristics of this ASR are not established."

(2) 809.10(a)(10)

21 CFR 809.10(f) – Drugs of Abuse OTC Collection systems

(f) The labeling for over-the-counter (OTC) test sample collection systems for drugs of abuse testing shall bear the following in language appropriate for the intended users:

(1) Adequate instructions for specimen:
- Collection and handling
- Preparation and mailing

(2) ID system to ensure specimens are not mixed up or misidentified at the lab, and user anonymity is maintained.

(3) Intended use(s), what drugs are to be identified, a quantitative description of the performance characteristics for those drugs (e.g., sensitivity and specificity), and the detection period.

(4) State that confirmatory testing will be done on all initially positive.

(5) 809.10(a)(4)

(6) Adequate instructions for obtaining test results from a person that can explain:
- Meaning of results
- Probability of false positive/false negative
- How to contact a trained health professional for additional information on interpretation or follow up counseling is desired.

(7) 809.10(a)(8)

Types of Labeling

- Device
  - Radiation Emitting Devices & Products
  - Prescription devices
  - Over-the-Counter
  - Home-Use
  - Investigational
  - Instrumentation – Manuals
  - Electronic (e.g., CD/DVD, web based)
  - Companion Diagnostic
- Patient
- Physician

Radiation Emitting Devices & Products (21 CFR Part 1000)

- Labeling of radiation-emitting products applies to medical devices which emit sonic, infrasonic, or ultrasonic radiation as the result of operation of an electronic circuit in addition to the general labeling requirements for medical devices.
- Includes electronic products that emit radiation either by design (e.g., X-ray equipment) or as a consequence of operation (e.g., television set), but exclude products that emit radiation as a result of the decay of a radioactive element or isotope (e.g., an ionization type smoke detector).
- Section 358 of the Radiation Control for Health and Safety Act (RCHSA) of 1968 authorizes the development of Federal standards for these types of radiation producing products.
- Performance standards
  - § 1010 – Electronic Products: General
  - § 1020 – Ionizing Radiation Emitting Products
  - § 1030 – Microwave And Radio Frequency Emitting Products
  - § 1040 – Light-emitting Products
  - § 1050 – Sonic, Infrasonic, and Ultrasonic Radiation-emitting Products

Prescription Devices

- Comply with 21 CFR 809.10
- Prominently displays ‘For prescription (home) use only’ or ‘For professional use only’ statement
- May be limited for use by specific users

Investigational Devices

- § 812.5 - investigational device or immediate package must bear a label with:
  - Name and place of business of the manufacturer, packer, or distributor;
  - Quantity of contents, if appropriate; and
  - Statement, "CAUTION -- Investigational device. Limited by Federal (or United States) law to investigational use."
- All relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.
- No false or misleading statements nor imply the device is safe or effective for investigated use.
- Research on laboratory animals use only, label must contain the following statement: "CAUTION -- Device for investigational use in laboratory animals or other tests that do not involve human subjects."
- Provide detailed information on device labeling in the investigational plan.
  - May vary depending on the device and the nature of the study.
  - Be sufficient to ensure stability for study duration (storage requirements, calibration procedures)
  - Bear sufficient directions for proper administration, and detail procedures to follow in the event of patient injury

Investigational Device Advertising

- Advertising:
  - Under § 812.7, a sponsor, investigator, or any person acting for or on behalf of a sponsor or investigator cannot:
    - Promote or test market an investigational device, until after FDA approval of device for commercial distribution.
    - Commercialize it by charging the subjects/investigators a price higher than necessary to recover costs
    - Unduly prolong an investigation
      - If investigational data won't support/justify a premarket approval (PMA), sponsor must promptly terminate the investigation.
    - Represent that an investigational device is safe or effective.
  - May advertise for research subjects to solicit their participation in a study
    - Newspaper, radio, TV, bulletin boards, posters, flyers, etc.
    - Should be reviewed by IRB to assure not unduly coercive or misleading
    - No claims should be made (explicitly or implicitly) that device is S&E for purposes under investigation or superior/equivalent to any other device

Over-The-Counter (Non-Prescription)

- Principal Display Panel 21 CFR 801.60
  - Portion of the label which is intended to be displayed, presented, shown, or examined under customary conditions for retail sales.
- Statement of Identity 21 CFR 801.61
  - The statement of identity of the device must be listed on the principal display panel.
  - List common name followed by a statement of principal intended action(s);
  - Indications for use must be listed in the directions for use; and
  - The statement must be in bold type, reasonably related in size to the most prominent printed matter on the display panel, and must be in lines generally parallel to the base of the package on which it rests.
- Net Quantity of Contents Statement 21 CFR 801.62
  - The label for packaged OTC device must contain
    - Statement of net quantity of contents in terms of weight, measure, numerical count; or a combination of numerical count and weight, measure, or size

Home-Use IVDs

- May require prescription, instrument, and documentation of training
- Examples:
  - Glucose
  - Cholesterol
  - Drugs of Abuse
  - Infectious Diseases (e.g., Hepatitis C, HIV)
  - Fecal Occult Blood
  - Reproductive (e.g., Ovulation, Pregnancy)
  - Prothrombin

Home-Use IVD Labeling

- Labeling Considerations
  - Acceptability dependant on whether labeling meets the criteria for "adequate directions for use" (Section 502(F)(1) of the Act & 21 CFR 801.5)
  - In compliance w/ adequate directions for use if 21 CFR 809.10 requirements are met (21 CFR 801.119)
    - 809.10 considered generally adequate for home-use IVDs, however primarily put into effect for professional-use IVDs
  - Written with sufficient detail/information and at a level to be understandable to a lay user (i.e., 8th grade) (Patient Labeling)
- Should also include:
  - Contact information for user questions (e.g., toll-free telephone number or address for written correspondence)
  - Mechanism for consumer awareness of labeling changes

Patient Labeling

- Any information associated with a device targeted to the patient or lay caregiver. It is intended to help assure that the device is used safely and effectively.
- This labeling may pertain to therapeutic, restorative, diagnostic, or cosmetic devices.
- Formats:
  - Brochures
  - Leaflets
  - User manuals
  - Video
- Is intended to be supplied, or given to and used by patients or their lay caregivers with or without accompanying professional counseling.
- May accompany devices intended solely for use by:
  - Physicians to operate (e.g., LASIK, breast implants, etc.)
  - Both physicians and patients or lay caregivers (e.g., PT/INR, Glucose monitoring devices, etc.
  - Operated solely by patients or their lay caregivers (e.g. Home-Use)

- Why is medical device patient labeling important?
- What are the general types of information that may be included in medical device patient labeling?
- When should you use medical device patient labeling?
- When is medical device patient labeling not usually necessary?
- What should you consider when identifying a method to distribute the medical device patient labeling?

Physician Labeling – IVD/IUOs

- Additional information directed to clinician who will have no opportunity to benefit from the IVD package insert
  - Meaning of test result(s)
  - Physician brochure (investigational devices)
  - Additional information deemed necessary to mitigate risks

Instrumentation

- 21 CFR 809.10(b)(6)
- Users Manuals
- Combined RUO/IVD Functionality – molecular diagnostics instruments
  - Labeling and marketing restrictions

Electronic Labeling

- Section 206 of MDUFMA amended Section 502(f) of the Federal FD&CA
  - Electronic version of paper labeling (e.g., package insert, users manual, etc.)
  - Complies with all applicable requirements of law as hard copy/paper version
  - Hard copy version should be available promptly upon request from user (esp. patient labeling) at no additional cost

Companion Diagnostics

- Comply with 21 CFR 809.10
- Cross-labeled with drug or biologic
- Clinical performance information from clinical trial (NDA/BLA)
- Patient and/or physician labeling may be required in addition to prescription labeling

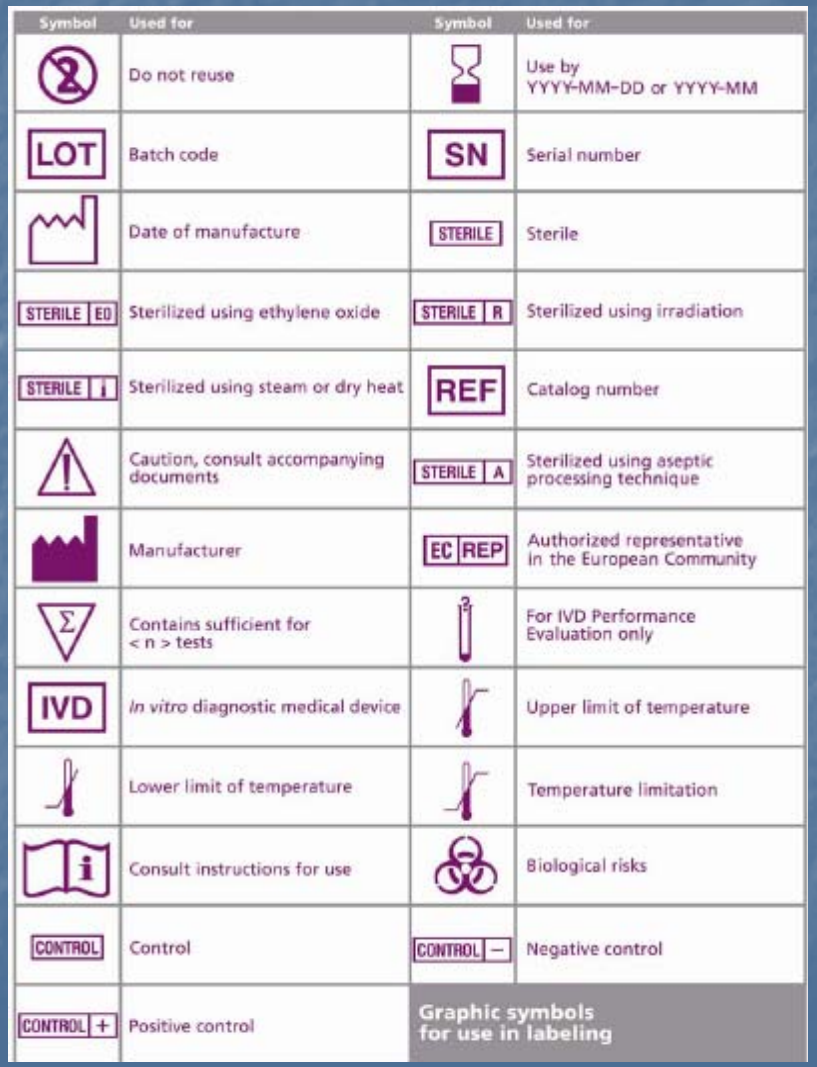
PI - Typical Order of Headings

- Proprietary Name
- Common/Established Name
- Intended Use
  - IVDs usually include Indications for Use
- Test Summary and Explanation
- Principle of the Procedure
- Device Description
- Materials/Reagents/Instruments
  - Supplied and not supplied
- Warnings/Precautions
- Storage & Handling of Reagents
- Indications of Instability
- Specimen Collection and Preparation
- Procedure (Instructions of Use)
- Calibration/Controls
- Quality Control
- Limitations of Procedure
- Expected Values
- Interpretation of Results
  - Include description of calculations)
- Summary of Analytical Performance
- Summary of Clinical Performance
- Troubleshooting
- References
- Warranty
- License Information
- Contact Information

Symbols

FDA Recognizes Selected ISO 15223 and EN 980 Medical Device Symbols

- ISO 15223, Medical Devices – Symbols to be used with medical device labels, labeling and information to be supplied
- EN 980, Graphical symbols for use in the labeling of medical devices



Symbol	Used for	Symbol	Used for
	Do not reuse		Use by YYYY-MM-DD or YYYY-MM
LOT	Batch code	SN	Serial number
	Date of manufacture	STERILE	Sterile
STERILE EO	Sterilized using ethylene oxide	STERILE R	Sterilized using irradiation
STERILE	Sterilized using steam or dry heat	REF	Catalog number
	Caution, consult accompanying documents	STERILE A	Sterilized using aseptic processing technique
	Manufacturer	EC REP	Authorized representative in the European Community
Σ	Contains sufficient for < n > tests		For IVD Performance Evaluation only
IVD	*In vitro* diagnostic medical device		Upper limit of temperature
	Lower limit of temperature		Temperature limitation
	Consult instructions for use		Biological risks
CONTROL	Control	CONTROL −	Negative control
CONTROL +	Positive control	Graphic symbols for use in labeling	

IVD Labeling changes – 510(k)

- Often pose the most difficult questions to be addressed by device manufacturers
- Should be careful with labeling changes
- If device changes result in need for label changes may need a new 510(k)
- If in doubt, ask OIVD

Additional Info Sources

- 510(k) database:
  - Search by 510 #, product code, device name, applicant name
  - Links to lots of useful dBs
  - Review templates after ~September 2003
  - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm
- Device Advice
  - CDRH specific! Lots of great background on pre- and post- market stuff
  - http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm
- CDRH Guidance Document database
  - For industry and FDA – what we look for or require for particular devices or topics
  - http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm

Labeling Guidance Documents & Information

Labeling - Regulatory Requirements for Medical Devices (FDA 89-4203)
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM095308.pdf

Write it Right
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM070771.pdf

Device Labeling Guidance #G91-1 (blue book memo)
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081368.htm

Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070801.pdf

Guidance on Labeling for Laboratory Tests; Draft
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm092795.pdf

Human Factors Principles for Medical Device Labeling
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM095300.pdf

Labeling Guidance Documents & Information

Electronic Labeling: Section 206 of the Medical Device User Fee and Modernization Act (MDUFMA) (New section 502(f) of the Federal Food, Drug, and Cosmetic Act) Electronic Labeling for Prescription Devices Intended for Use in Health Care Facilities - #G03-1
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm109203.pdf

Rx Labeling: Alternative to Certain Prescription Device Labeling Requirements
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm109203.pdf

Investigational Device Labeling Requirements
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm051480.htm

In Vitro Diagnostic Devices: Guidance for the Preparation of 510(k) Submissions - Appendix C - Points To Consider Regarding Labeling And Premarket Submissions For Home-Use In Vitro Diagnostic Devices:
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094567.htm

Does Your Product Emit Radiation?

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051504.htm

Thank You

Questions?

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