

# Drug and Biologic Labeling FDA Boot Camp: Training for Product Liability & Patent Lawyers American Conference Institute, Boston, MA

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- Label – a display of written, printed, or graphic information upon the immediate container of any article (21 U.S.C. 321(k))
- Labeling – all labels and other written, printed, or graphic matter upon any article or any of its containers or wrappers **or accompanying the article** (21 U.S.C. 321(m))
  - Need not be contemporaneous to “accompany” article
    - Can be sent later; textual relationship
      - Kordel v. U.S., 335 U.S. 345 (1948)
- Applies to drugs and biological products (42 U.S.C. 351(j))

- Product labeling is subject to review/approval as part of marketing application (instructions for use of drug)
- Labeling amendments submitted for review/approval as application supplements (e.g., new information)

- Public Health Service Act (42 U.S.C. 351(a)): the package label of a biological product must be plainly marked with:
  - Proper name of the licensed product
  - Name, address, and license number of manufacturer
  - Lot number
  - Expiration date

- Container label for blood/blood products (21 CFR 606.121):
  - Proper name of product prominently displayed, and modifier(s), if appropriate
  - Name, address, registration number
    - If licensed, license number of each manufacturer
  - Donor, pool, or lot number relating unit to donor
  - Expiration date, incl. day/month/year
    - If dating period for product is 72 hours or less, hour of expiration

- If intended for transfusion, appropriate donor classification statement (paid or volunteer) at least as prominently displayed as proper name
- Other specialized information as required
- Human Cells, Tissues and Cellular and Tissue-Based Products (HCT/P's) labeling requirements (21 CFR 1271)

- What Kind of “matter” constitutes prescription drug labeling?
  - Package Insert
  - Prescribing Information
  - Professional labeling
  - Directions Circular
  - Package Circular

- Must (21 CFR 201.56):
  - Contain summary of essential scientific information for safe and effective use
  - Be informative and accurate
  - Not be promotional, false, or misleading
  - Be updated when new information becomes available that causes existing labeling to be inaccurate, false, or misleading
  - Contain no implied claims or suggestions for uses for which evidence of safety and effectiveness is lacking
  - Be based on as much supporting human experience data as possible

- Nonprescription drugs marketed under
  - OTC new drug application (NDA), or
  - OTC drug monograph (no preapproval, but must comply with monograph regulation)
    - Generally recognized as safe and effective (GRAS/E) ingredients
    - No preapproval of label, but must comply with monograph as to content
      - e.g., indications, warnings, directions for use
- OTC labeling is meant to provide useful information for consumers

- Format and content requirements for OTC drug labeling (21 CFR 201.66):
  - Must have a **Drug Facts Label** on the outside container or wrapper of package, or immediate container label if none:
    - Active ingredient(s)
    - Purpose(s)
    - Use(s)
    - Warning(s)
    - Directions
    - Other information (e.g., other ingredients, tamper-evident statement)
    - inactive ingredients
    - Question or comments (optional)

# Sample OTC Drug Facts Label (FDA)

- Current FDA sample (“clear, simple, readable labeling”):
- **Drug Facts** - title
  - Active ingredient(s)** - including amount in each dosage unit
  - Purpose** - pharmacologic class
  - Use(s)** - indications
  - Warnings**
    - **Do not use** - absolute contraindications, when the product should not be used under any circumstances
    - Ask a doctor before use if you have** - warnings for persons with certain preexisting conditions and for persons experiencing certain symptoms
    - Ask a doctor or pharmacist before use if you are** - drug/drug and drug/food interactions
    - When using this product** - side effects that could occur and substances or activities to avoid
    - Stop use and ask a doctor if** - signs of toxicity and other serious reactions that would require consumers to stop using the product immediately
    - Pregnancy/breast-feeding warning**
    - Keep out of reach of children/Accidental overdose warnings**
    - Direction** - dosage and when, how, or how often to take
    - Other information**
    - Inactive ingredients**
    - Questions?** (Optional) - followed by telephone number

- A drug is misbranded if (21 U.S.C. 352):
  - Its labeling is false or misleading in any particular
  - its labeling fails to bear adequate directions for use
    - Directions under which layperson can use drug safely and for the purposes for which it is intended
  
- Other:
  - Does not include name and place of business of manufacturer, packer, or distributor, and accurate statement of the quantity of its contents
  - If word or statement or other required information not prominently displayed

- Misbranding subject to misdemeanor, or where intent to defraud or mislead a felony (FDCA 331, 333)
  - Misdemeanor can be strict liability
    - Responsible corporate officer doctrine (*United States v. Park*, 421 U.S. 658 (1975); *United States v. Dotterweich*, 320 U.S. 277 (1943))
- Factors to consider to determine misbranding:
  - Representations made or suggested by a statement or word, or
  - Extent to which the labeling or advertising **fails to reveal material facts** regarding consequences that may result from the use ... under the conditions of use prescribed in the labeling or advertising, or under customary and usual conditions of use

- For biologics approved under biologics license application (42 U.S.C. 351(b), unlawful to:
  - falsely label or mark any package or container of any biological product, or
  - Alter any label or mark on the package or container so as to falsify the label

- The **intended use(s)** of a product means the objective intent of the persons legally responsible for the **labeling** of drugs (21 CFR 201.128)
- May be shown by labeling claims, advertising matter, or **oral or written statements** by the manufacturer or its representative's)
- When manufacturer has knowledge/notice that drug is to be used for conditions, purposes, or uses other than the ones for which he offers it
  - he is required to provide adequate labeling which accords with such other uses to which the article is to be put
- FDA has stated intended use may be established by product labels and labeling, catalogs, brochures, audio and videotapes, Internet sites, or other circumstances surrounding the distribution of the product

- New intended uses
- Post-market Labeling Changes (new approved indications, warnings, etc.)
- Medication Errors
- Off-label Advertising and Promotion
- Practice of Medicine
- Dietary Supplement vs. Drug
- Medication Guides (21 CFR 208)

- Risk Evaluation and Mitigation Strategies (REMS)
  - Food and Drug Administration Amendments Act (FDAAA) (2008)
    - Strengthened authority to require/enforce postmarket studies and REMS
  - Pre-approval or post-approval
  - e.g., communication plans, required labeling changes
- Evolving Internet Uses/Policy (e.g., “Facebook Share” widgets)
  - See Untitled Letter to Novartis, 7/29/2010

- Cross-labeling of combination (drug-device-biologic) products
- Division of Drug Marketing, Advertising and Communications (DDMAC), CDER
- Advertising and Promotional Labeling Branch (APLB), CBER
- FDA, Federal Trade Commission (OTC drugs)

# Questions/Comments

- Happy to discuss any questions or comments
- Thank you