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Drugs and Biologics: Labeling

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Key Statutory Definitions
The Federal Food, Drug, and Cosmetic Act

- *Label* – "[A] display of written, printed, or graphic matter upon the immediate container of any article . . ."
- *Labeling* – "[A]ll labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article"
- We won't discuss the history of FDA regulation of "label" and "labeling" (see the appendix at the back of this handout – thanks to Gary Yingling)

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Some Basic Elements of the Package Label

- Name
- Place of business of manufacturer, packer or distributor
- Quantity of contents (weight, numerical count)
- Established name
- Adequate directions for use and warnings
- Compliance with USP
- Poison Prevention Packaging Act
  - ✓ e.g., child-resistant packaging

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Labeling

- Labeling may include:
  - instructions for use, posters, tags, pamphlets, circulars, booklets, brochures, instruction books, direction sheets, websites, and other promotional materials, external training materials or manuals
- Make sure standard operating procedures reflect these areas
  - the reach of the term “labeling” is broad, because it extends beyond mere physical association with the product

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Labeling *(cont'd)*

- However, the reach is not unrestricted
  - ✓ it must function as labeling
    - ➢ i.e., it must supplement or explain a product to help in the product's use
      - ❑ disease state communications, without product reference, and Continuing Medical Education activities are typically not considered labeling

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Labeling *(cont'd)*

- ✓ it must be supplied or disseminated by or on behalf of the manufacturer, packer or distributor
  - ➢ it's a control issue

- Everyone acting on behalf of the company is held to the same standards as the company and the company will be held responsible, even if the agent fails to conform to company policies
  - ✓ e.g., investigators, consultants, PR firms, marketing partners

Labeling Contents (General)

- Full established name
- Fair balance/Important Safety Information
  - ✓ risk information to balance positive claims
  - ✓ summary of most important risk information
  - ✓ comparable prominence
- Efficacy claims supported by “substantial evidence”
  - ✓ ideally, two adequate and well-controlled clinical trials

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Prescribing Information

Full prescribing information (FPI)

- We won't discuss the specific content requirements, such as drug name, dosage form, warnings, and initial U.S. approval date
  - ✓ any basic review of a label indicates the format and content
- Summary of scientific information for safe and effective use
- Informative and accurate
- Not promotional, false or misleading
- No implied claims or suggestions for use if evidence of safety or efficacy is lacking
- Based on data derived from human experience

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Did It Make It Into The Label?

- Final FDA-approved label controls the scope of post-market activities – this is the agreed-upon bible
  - ✓ indication(s)
  - ✓ population
  - ✓ efficacy
  - ✓ comparative claims
- If not, consider whether the exclusion was intentional
  - ✓ e.g., FDA did not consider the data presented to support its inclusion

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Risk Evaluation and Mitigation Strategies (REMS)

- When FDA determines that REMS is necessary to ensure benefits of drug outweighs its risk
- Labeling
  - ✓ medication guide – see 21 C.F.R. Part 208
  - ✓ patient package insert
  - ✓ communication plan

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Risk Evaluation and Mitigation Strategies (REMS) *(cont'd)*

- Can limit distribution
  - ✓ pharmacy/hospital
  - ✓ physician
  - ✓ patient monitoring
- Goal
  - ✓ reduce adverse outcomes from misuse or abuse of product while maintaining access

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Labeling for ANDAs

- Same as Reference Listed Drug (RLD) except:
  - ✓ name and address of manufacturer
  - ✓ carve out language
    - e.g., that protected by a patent or market exclusivity
  - ✓ changes allowed because of suitability petition
  - ✓ inactive ingredients

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Words Are Very Unnecessary

- Verbal statements that are not “labeling” can change a product’s intended use
  - ✓ e.g., trade show statements, workshops, seminars, hands-on demonstrations
- The intended use is what the product does
- Based on the objective intent of persons legally responsible for labeling
- Determined by expressions or circumstances surrounding distribution of product

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Comparative Claims

- While comparative claims are not illegal, FDA discourages the practice and has indicated that frequently such comparisons are incomplete and can be misleading
  - ✓ must be based on reliable and sound scientific data
  - ✓ should be a head-to-head testing with the competitive product in a well-controlled trial to support claim
- If a study compares two products, FDA recommends that it be presented in its entirety and must identify where the product could also be inferior, if applicable
  - ✓ minimize misbranding or unapproved product challenge

Comparative Claims *(cont'd)*

- Make sure it's a valid apples-to-apples comparison, for example:
  - ✓ claims are the same
  - ✓ populations/users are the same
  - ✓ correct information in context
  - ✓ substantiating data
    - □ multiple corroborating sources are preferable
  - ✓ if there are distinctions, note them
- The government may take enforcement action against companies that make comparative claims that promote an off-label use or offer a misleading statement about a competing product

Trade Shows and Exhibit Halls

- FDA considers exhibits for products at medical meetings and trade shows to be subject to all advertising and promotion regulations
- If an exhibit or display is created for a marketed product, claims must be limited to the approved uses, and must comply with FDA-authorized labeling

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Trade Shows and Exhibit Halls *(cont'd)*

- Company representatives who run the booths at medical meetings or trade shows should realize that any individual who approaches a booth and asks for more information may very well be an FDA employee or a competitor
- Typically, the company representative at an educational conference would be someone from Medical or Clinical Affairs
- Separate booths regarding commercial and investigational products to make clear the regulatory status of each product

Misbranding

- See 21 U.S.C. § 352 (or also known as section 502 of the FDC Act)
- Among other things:
  - ✓ the label or labeling is false or misleading “in any particular”
  - ✓ inadequate directions for use
  - ✓ inadequate warnings
  - ✓ lack of risk information
- We won’t discuss off-label promotion

Misbranding *(cont'd)*

- In short, not telling a complete, truthful story
- Ambiguity, misdirection, false comparisons to other products, and creating a false impression (including icons, symbols, URLs) are also ways to misbrand a product
  - ✓ every picture tells a story
- Some buzzwords that might raise FDA scrutiny (although not necessarily illegal)
  - all
  - none
  - more than
  - better
  - never
  - unique
  - best
  - most
  - "er"-ending comparisons
  - "safe" and "effective" for an investigational product

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Misbranding *(cont'd)*

- The agency has maintained (and the courts have upheld elsewhere) that false speech is not protected commercial speech
- Direct-to-consumer promotion is of particular concern to FDA
- Promotions that are highly visible increase risk
  - ✓ e.g., national medical conference, TV
- FDA has issued enforcement letters to companies that have product approvals, but where the promotions take the product outside the authorized use

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Misbranding *(cont'd)*

- Promotions that raise safety concerns are likely to trigger FDA action
- Verbal statements can be violative, so it's important to watch what your company employees or agents say, particularly at trade shows and medical conferences

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Ch-Ch- Changes

- New indication, claims, population, new relevant something that affects the label
- New safety information
- Prior Approval Supplement vs. Changes-Being-Effected Supplement vs. Annual Report
  - ✓ focus is on how significant the change is to have an adverse effect on the identity, strength, quality, purity, or potency of product that could affect safety or effectiveness

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One Thing Leads to Another

- Federal Trade Commission or Department of Justice enforcement
- Corrective advertising
- Loss of credibility with FDA and the marketplace
  - ✓ e.g., consumers, medical community
- Competitors will use it against you
  - ✓ e.g., trade complaint, Lanham Act lawsuit, National Advertising Division challenge
- Individual liability - prosecution
- Bad publicity
- Shareholder lawsuits

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One Thing Leads to Another *(cont'd)*

- Whistleblower complaints
- Product liability (evolving preemption doctrine)
- State prosecution
  - ✓ e.g., consumer deception
- Punitive damages
  - ✓ varies by state
  - ✓ compliance with FDA labeling requirements may bar recovery
- Diversion of $ from other projects to correct violative message

Off-label Reimbursement Implications

- False Claims Act enforcement
  - ✓ knowingly presents, or causes to be presented, a false or fraudulent claim for payment or approval
- Multi-million dollar settlements
- Corporate Integrity Agreements
- Potential criminal prosecution
- These are separate from FDA prosecution

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Product Liability – Preemption Doctrine (Generally)

According to U.S. Supreme Court:

- Generic – preemption applies (Pliva v. Mensing, 131 S. Ct. 2567 (2011)) – generic drug manufacturer cannot be sued under state law (over labeling warnings), because prohibited from changing labeling by FDC Act
- But Wyeth v. Levine, 129 S. Ct. 1187), said Federal law doesn't preempt state law lawsuit relating to liability (e.g., inadequate warning)
- Final chapter likely yet to be written
  - ✓ fact-specific cases might lead to different conclusions

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Recommendations

- Comply with FDA's labeling and promotional requirements, such as
  - ✓ required product information
  - ✓ truthful and balanced
  - ✓ be particularly aware of scrutiny relating to direct-to-consumer promotion
- Stick to the FDA-approved product labeling

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Recommendations *(cont'd)*

- File new applications or supplements for new indications or if you want to make a legitimate comparative claim
- Be careful about oral statements
- Don’t get hung up with titles, such as Medical Communications
  - ✓ FDA is more concerned with content and message
  - ✓ educate internally about role difference and separate training for respective groups

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Recommendations *(cont'd)*

- Make clear what's "approved" and what's "investigational"
- Watch the wording and the spin
  - ✓ problem words:
    - ➢ revolutionary!
    - ➢ best ever!
    - ➢ more effective than X, Y, and Z!

Recommendations *(cont'd)*

- Carefully consider the claims you want to put in the label and which you can demonstrate – this is the labeling FDA will review
- If FDA rejected a claim during the regulatory review process, you would be ill-advised to promote that claim
- Always have substantiation for claims
- Do not draw conclusions of safety or efficacy (including quotes from investigators or company executives) if unapproved product
- Tell a complete and accurate story

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Recommendations *(cont'd)*

- Be careful about symbols, logos, or graphics that can also get a company into trouble with intended use issues
- Make sure there is consistency concerning what you instruct and what is done in reality and label is current
  - ✓ you might need to update the package insert based on doctor usage and new information
- Disclaimers or qualifying statements are helpful but won’t eliminate risk if the whole promotion, when viewed in full and in context, is violative

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Recommendations *(cont'd)*

- All materials disseminated should be reviewed internally
  - ✓ accuracy and appropriateness of information
  - ✓ balance of information and regulatory compliance
  - ✓ education vs. promotional message
- Establish procedures before distribution and a team to review all promotional materials, regardless of the intended audience or the form of the promotion
  - ✓ e.g., an internal review checklist that requires signoff by appropriate personnel and audit to ensure compliance

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Recommendations *(cont'd)*

- Include individuals from:
  - ✓ Medical Affairs
    - e.g., looking at supporting medical references, study methodology, adverse events, risk presentation information
  - ✓ Regulatory Affairs
    - e.g., review against FDA-approved label and agency communications, presentation of risk information, regulatory compliance
  - ✓ In-house counsel
    - e.g., consideration of product liability risk, minimizing competitor challenge, regulatory compliance
  - ✓ Outside regulatory counsel (if appropriate)

Recommendations *(cont'd)*

- Remain vigilant in monitoring promotional activities
  - ✓ keep up with enforcement trends by looking at past FDA enforcement letters
  - ✓ monitor what FDA is doing to competitors
- Be aware of your marketing partner's promotional activities relating to your product
- Train employees and third parties you employ about company policies and monitor/audit them
  - ✓ don't want renegade individuals getting the company in trouble
  - ✓ audit internally to make sure everyone is on the same page

Recommendations *(cont'd)*

- Ensure review by company's foreign and domestic regulatory department (e.g., foreign marketing practices), where marketing piece is generated by foreign entity for U.S. publication
- In isolation, each proposal might not raise FDA scrutiny
- But when all activities are taken together, the agency could argue that there was a concerted unlawful promotional campaign

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Appendix - Statutes

- The Federal Food and Drugs Act of 1906
  - ✓ labeling statute
- The Federal Food, Drug, and Cosmetic Act of 1938
  - ✓ defined
    - ➢ label
    - ➢ labeling
  - ✓ drug
    - ➢ new drug

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Statutes

- The Durham-Humphrey Amendments of 1951
  - ✓ created prescription and over-the-counter (OTC) classes
  - ✓ regulation of prescription drug labeling
- The Kefauver-Harris Drug Amendments of 1962
  - ✓ regulation of prescription drug advertising
- The Drug Listing Act of 1972
  - ✓ drug establishments must provide copies of labels

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Statutes *(cont'd)*

- FDA Modernization Act of 1997
  - ✓ can use "Rx only"
  - ✓ allowed "FDA-Approved" labeling
- FDA Amendments Act of 2007
  - ✓ Risk Evaluation and Mitigation Strategies (REMS)
- FDA Safety and Innovation Act (FDASIA) of 2012
  - ✓ study benefits of electronic labeling versus paper
  - ✓ develop prescription drug container labels for blind or visually impaired

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Relevant Regulations

- 21 C.F.R. Parts 201 and 202 (labeling and Rx drug advertising)
- 21 C.F.R. Part 312 (IND)
- 21 C.F.R. Part 314 (New Drugs)
- 21 C.F.R. Part 601 (Biologics)

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