Introduction to Compliance with FDA Labeling and Advertising Requirements

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FDA History

- Basic function of government
- Oldest and most comprehensive consumer safety agency
- FDA regulates about 25 percent of consumer economy; budget of only approximately \$1billion

FDA Place in Government

- Part of Public Health Service within
 Department of Health and Human Services
- Statutory creation in 1988 (section 903)
- Relatively -- but not completely -- free of political influence by Administration
- Intense congressional oversight

FDA Mission

- To promote the public health through timely approvals
- To protect the public health through enforcement of the law
- Fundamental tension
- Agency employees take jobs seriously, have enormous practical power

Statutory Framework

- History
 - Responses to public health crises
 - PDUFA and FDAMA exceptions
- 1938 Act
 - Definitions
 - Prohibited acts
 - Substantive requirements
 - Rulemaking and miscellaneous provisions

Regulations and Guidances

- Title 21 of the C.F.R.
- Guidance documents, letters to industry, enforcement letters, internal manuals, etc.
- www.fda.gov

The Compliance Challenge

- Appropriate business rationale
- FDA issues
- ACCME issues
- AMA Guidelines on Gifts to Physicians
- Fraud and abuse
- Best price
- Product liability
- Lanham Act

Definitions

- Labeling
- Advertising
- Non-promotional communications

Definition of "Labeling"

- "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"
 - Section 201 (m)
- "Accompanying" has a broad meaning
 - U.S. v. Kordel, 335 U.S. 345 (1948)

"Labeling" Revisited

- FDA holds that labeling encompasses
 - Any written, printed or graphic material
 - Containing drug information
 - Disseminated by or on behalf of the manufacturer of that drug
 - For use by healthcare professionals

Examples of "Labeling"

- Brochures, detail pieces, bulletins
- Literature reprints
- Films, videos, CD-ROM disks
- PowerPoint presentations
- "Homemade" sales aids
- Automated telemarketing
- Press releases

Definition of "Advertising"

- Not defined in statute
- 1938 Act conferred jurisdiction over all advertising of all FDA-regulated products on FTC
- 1962 Amendments transferred jurisdiction for advertising of Rx drugs only to FDA
- Change was in response to FDA's lack of power to control this "advertising"

Labeling vs. Advertising

- FDA regulation purports to distinguish them
 21 C.F.R. 202.1 (1)
- "Advertising" means advertisements in publications or broadcast through audiovisual media such as radio, television, and telephone communication systems
- "Labeling" is everything else!

Oral Statements as "Labeling"

- FDA has asserted that oral statements by sales representatives are "labeling"
 - Never litigated
- FDA has asserted that speeches in CME programs and lectures are "labeling"
 - Never litigated

Non-Promotional Communications

- Responses to unsolicited requests
- Support for continuing medical education
- Reporting scientific results
- Market research
- Meetings with investigators and consultants

Requirements for advertising and promotional labeling

- Claims must be consistent with prescribing information
- No false or misleading statements or omissions
- Materials must fairly balance benefits and risks
- Substantiation
- Labeling accompanied by prescribing information; ads must include "brief summary"

Consistency With Prescribing Information

- Approved conditions of use, including
 - Indications
 - Dosages
 - Patient populations
- Effectiveness and safety claims
- Responses to unsolicited requests
- Pre-approval promotion (IND regulations 21 C.F.R. § 312.7)

Consistency (continued)

- FDAMA process for off-label reprints
 - Supplement requirement
 - Prior submission to FDA
- Washington Legal Foundation litigation

Truthful and Not Misleading

- A drug is misbranded if its labeling is "false or misleading in any particular" (Section 502 (a))
- True statements can be misleading (e.g., if they lack clinical significance)
- Material omissions can make otherwise "true" representations misleading (Section 201 (n))
- Disclaimers can be inadequate
- Requirements apply to all reasonable interpretations of a claim
- Checklist in advertising regs. (section 202.1)

How Claims Can Mislead

- Factors that make claims misleading:
 - Lack of adequate basis for comparative claims
 - Reliance on inadequate studies
 - Manipulation of data, statistical analysis
 - Lack of sufficient emphasis on adverse effect information
 - Promotion of uses beyond approved NDA

Fair Balance

- Balanced presentation of safety and effectiveness information
- Applies to entire piece and to individual segments
- Comparable prominence and readability

Substantiation

- Claims must be supported by substantial evidence
- Ordinarily, adequate and well-controlled head-to-head studies are required; Number needed
- In vitro comparisons
- Insert-to-insert comparisons

Substantiation (continued)

- Clinical study design issues (e.g., power, blinding, dosages, concomitant therapies)
- Presentation of results
- Clinical and statistical significance required
- Other principles also apply (e.g., consistency with prescribing information)
- Healthcare economics

Direct to Consumer Advertisements

- DTC ads for Rx products subject to same requirements
 - Print advertisements (brief summary)
 - Broadcast advertisements
 - Must have information about "major side effects and contraindications"
 - Must present brief summary or make "adequate provision" for dissemination of full product labeling
- Effect on learned intermediary doctrine

Mandatory Advertising Contents

- Drug is misbranded if advertising fails to contain:
 - Established name
 - Ingredient information
 - Brief summary of side effects,
 contraindications, and effectiveness
- Reminder advertisements

FDA Review of Promotion and Advertising

- Advertising and promotional labeling are *generally* not pre-approved but submitted at time of "first use"
 - Exceptions: launch materials; accelerated approval; FDA special requirement
- FDA relies on after-the-use enforcement to address violations

Enforcement

- FDA's enforcement tools
 - Untitled letters
 - Warning letters
 - Corrective advertising
 - Dear healthcare professional letters
 - Preclearance
 - Consent decrees
 - Criminal penalties

Enforcement

- What FDA looks for
 - Product specific
 - Recurring deviations
 - Consistent theme across different media
 - Level of public health risk
 - Company
 - Recurring deviations across product lines

Enforcement

- FDA monitoring
 - Review of materials submitted by company at "first use"
 - Complaints from competitors, health care professionals, plaintiff lawyers
 - Media surveillance
 - Attend healthcare professional meetings

Current Issues

- First Amendment law
- Dissemination of reprints for unapproved uses
 - FDAMA
 - Recent court cases
- Preapproval promotion and advertising
- Internet promotion
- Scientific and educational activities