Advertising & Promotion of Prescription Drugs, Biologics and Medical Devices
Sources of Regulation

- §502(n) added to the FD&C Act in the Kefauver-Harris Amendments in 1962, codified at 21 USC §502(n):
  - Gives FDA specific authority over the advertising of prescription drugs
    - Including labels, labeling, advertising, and promotional activities (such as trade show demonstrations, oral presentations by sales representatives, video and audio conferences, meetings, and press releases).
  - Applies to prescription drugs, biologics, medical devices and animal drugs
  - Rules codified at 21 CFR address standards for prescription drug advertising
Sources of Regulation

- Products that are supported by advertisements and promotional labeling that are false or misleading in any particular are misbranded under 21 USC §§352(a), (n) and are prohibited from entry into commerce under 21 USC §§331(a) and (k)
- Anti-Kickback Statute, §1128B(b) of the Social Security Act (SSA) makes it a criminal offense for anyone who knowingly and willfully solicits or receives any remuneration (kickback, bribe, rebate) to induce referrals or services reimbursable by any federal healthcare program.
Sources of Regulation

- **False Claims Act, 31 USC §3729**
  - OIG and DOJ indirectly regulates off-label promotion where that leads to false claims for reimbursement under a Federal program.

- **§5 of the Federal Trade Commission Act**

- **Lantham Act, 15 USC §1125(a)**
  - Competitors can bring action against a company that makes unsupportive claims that lead to competitive hard.
  - Courts struggle with Latham Act vs. FDCA preemption

- **State Unfair Competition and Consumer Deception Laws.**
Jurisdiction

● FDA
  ● Within FDA, each center regulates the advertising and promotion of the products it regulates.
  ● Most Centers follow CDER, which regulates drug promotion through its Office of Prescription Drug Promotion (OPDP), formerly known as the Division of Drug Marketing, Advertising and Communications (DDMAC).

● FTC
  ● §5 of the FTC Act gives overlapping jurisdiction, resolved by MOU between FDA and FTC.
  ● Regulates OTC drug advertising as well as all non-restricted medical device advertising and promotion.
Advertising vs. Labeling

- Labeling
  - §201(m) of the FD&C Act (21 USC §321(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) accompany such article.”
    - Supreme Court held “accompanying such article” in the “labeling definition” applies to any materials that supplement or explain the drug.
    - Court held that “[n]o physical attachment one to the other is necessary. It is the textual relationship that is significant.”
Advertising vs. Labeling

Labeling (cont.)

- See also, U.S. v. Articles of Drug…5906 Boxes, 745 F.2d 105 (1st Cir. 1984), cert. denied, 470 U.S. 1004 (1985) (noting index cards provided to doctors are labeling because the cards explained the drug).
- Regulations define “labeling” as wide variety of written, printed or graphic matter that bears a textual relationship with a drug or device, such as written materials handed out or otherwise distributed by the company or its representatives.
- As a practical matter, FDA regulates labeling and advertising in the same matter.
Advertising vs. Labeling

- Labeling (cont.)
  - FDA considers oral statements to be “labeling”
  - Generally two (2) types of “labeling”
    - The FDA-approved Label (“The Label”) and
    - “Promotional Labeling”
Advertising vs. Labeling

Labeling (cont.)

- The FDA-approved Label (“The Label”)
  - Intended for healthcare professionals
  - Submitted with pre-approval application (NDA, BLA, PMA)
  - Most robust benefit-risk statement for drug (can include MedGuide (required), “Patient Package Insert” provided by Mfr. (optional), etc.)
Advertising vs. Labeling

- Labeling (cont.)
  - “Promotional Labeling”
  - accompanies the product or is otherwise related to the product
  - No pre-approval required, but submitted at time of distribution
  - Promotional Labeling must be accompanied by a copy of the full product label.
  - Content must be consistent with the FDA-approved label
Advertising vs. Labeling

- Advertising
  - not defined by statute or regulation but includes such items as “advertisements published in journals, magazines, other periodicals, and newspapers, and advertisements broadcast through media such as radio, television and telephone communication systems.” 21 CFR §201.1(l)(1)
  - Unlike labeling, advertisements need only include a “brief summary” relating to the side effects, warnings, precautions and contraindications of the product, but not full product labeling.
Advertising vs. Labeling

- Advertising (cont.)
  - Brief Summary
    - Can be lengthy and may contain most of the information found in the package insert
  - Multiple types of promotional labeling and advertising subject to FDA oversight:
    - Product claims re: safety and efficacy
    - Reminder labeling and advertising (contain only a reference to drug name or characteristic, not risk information needed)
    - Help seeking labeling and advertising (general information on disease, encouragement to talk to you doctor; if general, FTC jurisdiction, if drug-specific, FDA jurisdiction)
Standard of Review

- Except in certain circumstances, FDA can not require pre-clearance of advertising and promotional materials.
- Submission to OPDP review is voluntary.
  - Most companies submit materials at prior to “first use” given (i) the cost of the materials’ development and risk of it being pulled later; (ii) prior approval provides insight on how OPDP views product claims for future campaigns.
  - OPDP will give advisory comments that are binding against the FDA absent a “change of opinion” letter and a reasonable time for correction.
Standard of Review

Exceptions where Pre-Submission is Required:

- “extraordinary circumstances” where FDA has received information that product poses significant public health risk;
- Fast Track designed products;
- Accelerated approval, 21 CFR 314 Subpart H
- Instances of repeated violations from a company where FDA, as part of voluntary corrective action plan, imposes pre-clearance ranging from six months to two years.
Standard of Review

- False and Misleading
  - that a product is misbranded if it is false or misleading in any particular;
  - 21 USC §321(n) states that whether a drug’s labeling or advertising is misleading should take into account “not only representations made or suggested” but also “the extent to which the labeling or advertising fails to reveal facts material in light of such representation”
  - Affirmative statements
  - Material omissions
  - Both specific statement and overall impression (size, location, graphics, etc.)
Standard of Review

- False and Misleading
  - All product claims must be supported by substantial evidence or, in the case of advertisements, substantial clinical experience. 21 CFR §201.1(e)(4)(ii)(b) and (c).
Standard of Review

● Fair Balance
  • All advertisements must have a fair balance “between information related to side effects and contraindications and information related to effectiveness of the drug.” 21 CFR §202(e)(5)(ii)
  • Must be “true statement
  • Includes consideration of content, format and context
  • Lack of fair balance leads to inadequate risk communication, overemphasis on benefits.
  • High volume Warning Letters on this point
Standard of Review

- Providing Risk Information in Advertisements – the “Brief Summary”
  - 21 CFR §202.1(e): advertisements must contain “a true statement of information in brief summary related to side effects, contraindications and effectiveness”
  - Applies to advertisements (e.g., medical journals)
  - Four categories: side effects, warnings, precautions, and contraindications required
  - Must be printed adjacent to the advertisement; does not relieve company from “fair balance”
Standard of Review

- False & Misleading or Unfair Balance Examples:
  - Unsubstantiated claims that drug is better, more useful, safer or has fewer side effects;
  - Unsupported comparative efficacy claims;
  - Selective use of scientific data, statistical findings, or expert statements;
  - Misrepresentation of size or scope of study (use of animal data)
  - Relying on data related to different dosage forms from approved product.
Types of Product Advertising & Promotion

- Pre-approval Promotion
  - Safety and efficacy claims prohibited except for
    - “full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media.” 21 CFR §312.7(a).
    - Limited pre-launch “coming soon” advertisements that do not combine name + indication
    - FDA discouraged pre-approval promotion of products likely to receive a black box warning.
Types of Product Advertising & Promotion

- Press Releases
  - Potential conflicts between “full disclosure” required under the Securities and Exchange Act of 1934, administered by the SEC, and FDA’s prohibition on pre-approval promotion
  - Example: Upjohn Co. SEC release on clinical trials on minoxidil (hair loss). Warning letter asserting misbranding.
  - Review of both pre and post approval advertisements
Types of Product Advertising & Promotion

- Reminder Advertisements
  - Piece must contain the proprietary name of the drug product and the established names of all active ingredients.
  - May include information on: dosage form, quantity of pkg. contents, price, name/address of mfr., and other written, printed or graphic matter that contains no information relating to the drug product.
  - Examples: pen, note pad, magnets, scrubs, mugs, etc.
  - Exempt from “brief statement” requirement
  - May not make express or implied claims re: safety or efficacy of the drug product.
Types of Product Advertising & Promotion

- Direct-to-Consumer Advertisements (DTC)
  - Two types:
    - print advertisements and
    - broadcast advertisements
  - Primary difference between the regulation of print and broadcast advertisements is the nature, extent, and formatting of risk information that must be present in the advertisement
  - FDA regulations adjusting to greater emphasis on patient education and input
  - PhRMA also issued principles on DTC advertising
Types of Product Advertising & Promotion

- DTC Print Advertisements
  - Must be fair and balanced, include brief summary
  - Must companies use full package insert for brief summary
  - FDA encouraged consumer-friendly language
  - Abbreviated label, however, could have product liability implications
Types of Product Advertising & Promotion

- DTC Broadcast Advertisements
  - Include advertisements broadcast through television, radio, or telephone, etc.
  - Must “include information relating to the major side effects and contraindications of the advertised drugs in the audio or audio and visual parts of the presentation…” 21 CFR §202.1(e)(1). This is referred to as the “major statement.”
  - Must include a “brief summary” unless “adequate provision is made for dissemination of the approved or permitted package labeling in connection with the broadcast presentation”
Types of Product Advertising & Promotion

- DTC Broadcast Advertisements (cont.)
  - FDAAA (2007) gave FDA authority to require pre-submission of DTC broadcast ads.
  - 2012 Guidance entitled “Direct-to-Consumer Television Advertisements: FDAAA DTC Television As Pre-Dissemination Review Program”
    - 6 Categories of high-risk advertisements requiring pre-dissemination review, including products with higher-than-usual risks and contexts where ads are more likely to mistake the product’s risks
Types of Product Advertising & Promotion

- DTC Internet Promotion
  - FDA holds web-based promotion to the same standard as print advertising
    - External websites paid for or controlled by the company render the company responsible for the content on those sites.
    - Insufficient to merely link to the full prescribing information; there must be a brief summary.
  - Social Media Platform Guidance (2014):
    - “[if] an accurate and balanced presentation of both risks and benefits of a specific product is not possible within the constraints of the platform, then the firm should reconsider using that platform.”
Types of Product Advertising & Promotion

- DTC Internet Promotion (cont.)
  - Guidance entitled “Internet/Social Media Platforms: Correcting Independent Third-Party Misinformation about Prescription Drugs and Medical Devices” (June 2014)
    - Does not require firms to correct third party information, but permits them to do so.
    - If correction is sought, the corrective action must correct all the misinformation within a clearly defined portion of the forum at that time.
    - Corrective information must be presented in manner connected to misinformation; affiliation with product disclosed; and cannot have promotional tone.
Types of Product Advertising & Promotion

- **Disease Awareness Ads**
  - Discuss particular disease or health condition
  - Prohibited from mentioning drug
  - Directed at healthcare providers or consumers

- **Help Seeking Ads**
  - Subset of Disease Awareness Ads
  - Not considered product promotion or labeling (1) because not linked to specific product and particular indication and (2) not intended to promote drug
  - Directed at consumers, encouraging them to consult a healthcare provider.
Types of Product Advertising & Promotion

- Price Advertising
  - Pharmacy or similar entity may promote price of product.
  - Regulated as reminder ad; may not contain anything about the drug’s safety or efficacy or indications for use (21 CFR §200.200(a)(1))
  - Must explain the quantity for the price, including all fees
Types of Product Advertising & Promotion

- Healthcare Outcomes Effectiveness Research (HCOER)/Pharmacoeconomic Claims
  - Economic benefits claims for a product, often made to formulary committees.
  - Regulated as labeling and promotion when issued to providers.
  - FDA Guidance forthcoming, but Warning Letters issued to unsubstantiated claims of cost effectiveness.
  - Multiple Notice of Opportunity for Public Comment and Affordable Care Act established Patient-Centered Outcomes Research Institute (PCORI) to conduct comparative effectiveness research.
Types of Product Advertising & Promotion

● Comparative Claims
  ● Claims comparing the safety and efficacy of a drug to another agent must support this claim with substantial evidence (same standard for any efficacy claim)
  ● Must be apples-to-apples comparison (both approved for same indication on label, same dosage regimen, same dose range)
  ● Implied superiority claims subject to enforcement actions; expecting to increase with HCOER
Types of Product Advertising & Promotion

- Off-Label Promotion
  - Promotion of an approved drug product for an indication for which it is not approved
  - FDA does not regulate the practice of medicine and, accordingly, does not regulate off-label use of a drug
  - FDA does, however, regulate off-label promotion of the drug as doing so undermines the incentive to seek pre-marked approval for these (potentially unsubstantial) indications
Types of Product Advertising & Promotion

- Off-Label Promotion (cont.)
  - “Safe Harbor” at 21 CFR §99.101(a)
    - information about the safety, efficacy, or benefit of a drug for a use not described in the approved labeling may be disseminated and shall (1) be about a drug already approved; (2) be in the form of an unabridged reprint; (3) not post a significant health threat; (4) not be false or misleading; (5) not be derived from clinical research conducted by another manufacturer; and (6) not be letters to the editor, abstracts, phase 1 publications, and publications containing little substantive discussion (observations of fewer than 4 people are not sound and are precluded).
Types of Product Advertising & Promotion

- Off-Label Promotion (cont.)
  - Considerable Industry concern that FDA’s restrictions on off-label promotion have burdened the 1st Amendment’s guarantee of freedom of speech.
  - Several Cases highlight this concern:
    - Sorrell v. IMS Health, Inc. 131 S. Ct. 2653 (2011)
    - U.S. v. Caronia, 703 F.3d 149 (2d Cir. 2012)
Types of Product Advertising & Promotion

- Off-Label Promotion (cont.)
  - FDA asserts that it remains free to take enforcement action outside the “safe harbor”
  - Will focus primarily on actions combined with speech that reflect an intent to promote off-label uses of drug products.
  - Remains one of the most frequent compliance/enforcement actions taken by FDA.
Scientific Exchange

- Continuing Medical Education (CME)/Educational and Scientific Events
  - FDA encourages exchange of information at conferences, peer-reviewed journals, but monitors for independence.
  - FDA does not object to unsolicited requests for off-label information on unapproved uses.
    - Inquires handled by medical affairs (not marketing), logged.
Scientific Exchange

- Use of Medical Science Liaisons (MSLs) to Communicate with Physicians
  - Medical or scientific expertise employed to consult directly with physicians; hard to distinguish at times from “detailing” if not careful.
  - Some exchanges can lead to enforcement actions (content and context important).
Biologics and Device Variants

- **Biologics**
  - Same substantive rules that apply to prescription drug advertising and promotion apply to biologics advertising and promotion
  - CBER Procedural Guidance document articulates four main criteria: (1) not false and misleading; (2) consistent with approved package insert; (3) fair balance; and (4) brief summary

- **Medical Devices**
  - CDRH regulates advertising for “restricted devices”
  - FTC regulates advertising of all other devices, applies “competent and reliable scientific evidence” standard.