Regulation of Drug Marketing

Presented by:

Jur Strobos MD JD

Potomac Law Group

jstrobos@potomaclaw.com

FDLI

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

Outline

- Federal Food, Drug, and Cosmetics Act (FDCA)
  - Prescription Drugs
  - “Promotional” Labeling
  - Office of Prescription Drug Promotion (CDER)
  - Advertising and Promotional Labeling Branch (Biologics/CBER) ‘Applebee’
  - Direct Enforcement
- AntiKickback and False Claims
- Over-the-Counter Drugs
- FDA Accommodates the First Amendment
- Conclusion

FDLI
Food and Drug Law Institute

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

Learning Objectives

- What is a New Drug?
- What is “Consistent with Labeling”?
- Fair Balance
- Belated Application of the First Amendment
- Remedies

FDLI
Food and Drug Law Institute

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

Step One – Federal Food, Drug, and Cosmetics Act

- How is a "new drug" defined in FDCA?
- What is labeling?
- What are adequate directions for use?
- What is "intended use"?
- FDCA Section 505(d)
  - FDA approves intended use which is embodied in labeling
  - Intended use is based on "adequate and well-controlled" investigations
  - What is substantial evidence to support intended use?

FDLI Food and Drug Law Institute

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

Step Two - OTC Drugs

"Old" drugs live on

- Two different types of OTC Drugs
  - Drug Efficacy Study Implementation
    - Monograph
  - OTC Switch
- Approved labeling/intended use & components
- Joint jurisdiction with Federal Trade Commission
- Trade complaints (National Advertising Division)

- Pre-1936
- Prescription Drug Wrap-Up
- Drugs missed in DESI
- Still in draft monograph

FDLI Food and Drug Law Institute

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

Step Three – Enforcement and Penalties

- Phone calls, emails, letters of inquiry
- Warning and Untitled Letters
- Misbranding and Prohibited Acts
  - Injunctions and Consent Decrees
  - Seizures
  - Criminal Penalties
  - Individual, Corporate, and *Park* Doctrine Liability
  - Warning and Untitled Letters
  - Debarment
  - Corrective Actions, Dear Doctor Letters, and ”Voluntary” Recalls
  - Compliance Integrity Agreement
- Import Alerts and Detention
- False Claims Act
- AntiKickback
- Unfair Competition
  - Federal Lanham Act
  - State Laws
  - NAD Complaints
- Consumer Confusion
  - Private Rights of Action
  - State Laws

FDLI
Food and Drug Law Institute

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

Step Four – Problems Emerge

- Scientific and Educational Activities (Continuing Medical Education)
- Grants and Charitable Contributions
- Support for External Academic or Medical Organizations
- Investigator Initiated Research
- Unsolicited Requests and Medical Science Liaison
- Good Reprint Practices
- First Amendment Rights and *Central Hudson*

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

What is a Drug?

- Drug (§ 201(g)(1))
  - "(B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man
  - "(C) articles (other than food) intended to affect the structure or any function of the body of man"
- What is a drug?
  - Active Pharmaceutical Ingredient (API)
  - Intended Use
    - "Objective intent of the persons legally responsible for the labeling of drugs."[1]
    - Whatever the person proposing a commercial transaction states about the drug in labeling.

Pure Food and Drug Act criminalized fraud not new APIs

[1]21 CFR § 201.128

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

Definition of "Labeling"

- "The term 'labeling' means all labels and other written, printed, or graphic materials
  - (1) upon any article or any of its containers or wrappers, or
  - (2) accompanying such article
- *Kordel v. U.S.*, 335 U.S. 345 (1948)
  - In this case the drugs and the literature had a common origin and a common destination. The literature was used in the sale of the drugs. It explained their uses. Nowhere else was the purchaser advised how to use them. It constituted an essential supplement to the labelattached to the package. Thus the products and the literature were interdependent, as the Court of Appeals observed.
- By operation of the statute, any direct or indirect statement from a sponsor about the drug has the potential to become labeling and hence, an intended use or claim to an effect.
- A change in "intended use" makes the drug a wholly new drug.

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

"Misbranding"

- FDCA § 502 [352]
  - A drug or device shall be deemed misbranded –
    - (a) If its labeling is false or misleading in any particular
    - (f) Unless its labeling bears
      - (1) adequate directions for use[1]
    - (n) If an article is alleged to be misbranded because the labeling of advertising is misleading, in determining whether the labeling or advertising is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also to the extent to which the labeling or advertising **fails to reveal facts** material in light of such representation.
- Title 21 CFR § 202.1(e)(5)(ii), (6) defines the latter as "lacking in fair balance."

[1]Consider lay use – any drug with a significant risk or complicated benefit is considered *ipso facto* unable to have adequate directions for use. This form is misbranding is waived if Rx and accompanied by package insert.

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

What happens if misbranded?

- FDCA § 301 [331] PROHIBITED ACTS
  - The following acts and the causing thereof are hereby prohibited:
    - (a) The introduction or delivery into interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded.
- FDCA Penalties for a prohibited act (in brief):[1]
  - Seizure of the goods § 304(a)
  - Injunction § 302
  - Criminal Fines and Imprisonment § 303
  - Civil Penalties § 303 (Recent Addition)

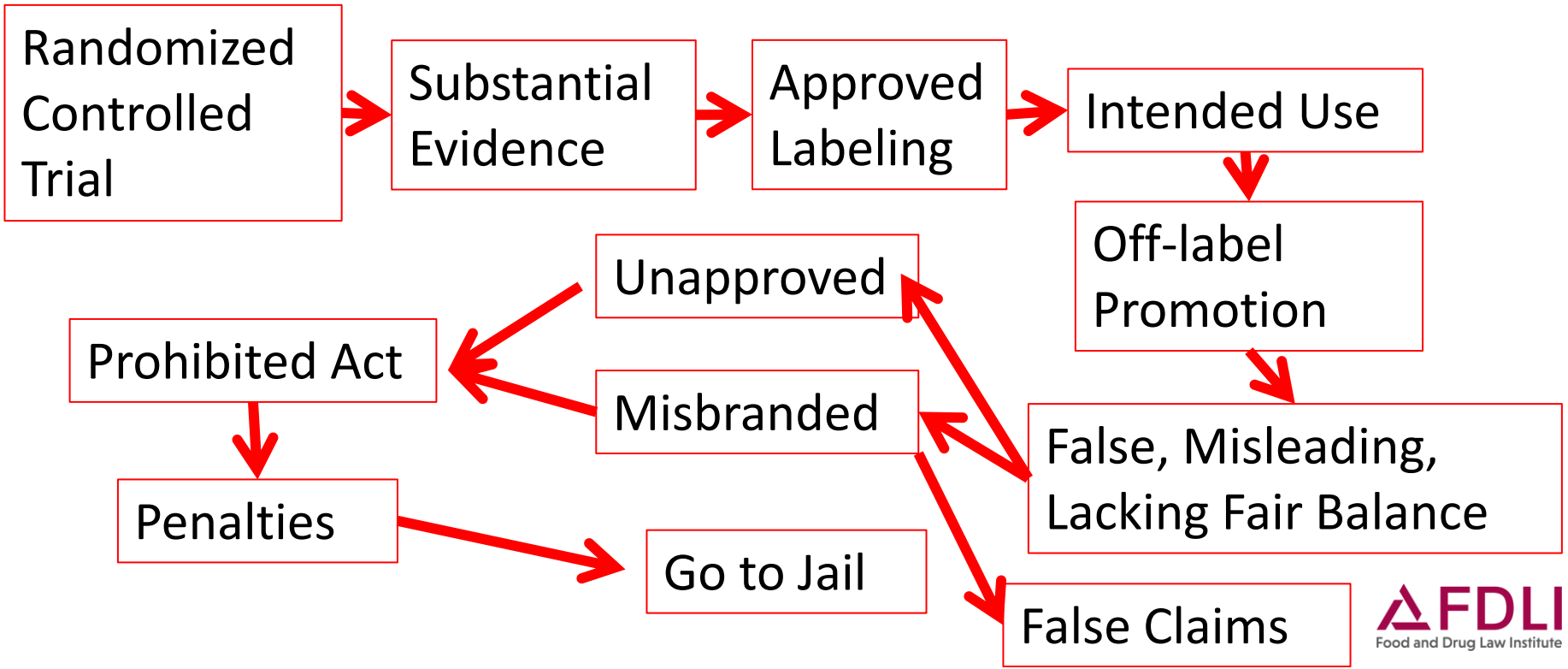
[1]Next lecture

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

False, misleading, or lacking in fair balance – what is the standard for "truth"?

- FDCA § 505(a)
  - No new drug may be introduced into commerce unless approved upon application.
- FDCA § 505(d)
  - Secretary shall issue an order refusing approval if "such labeling [as submitted] is false or misleading in any particular" including if:
    - (5) "[T]here is a lack of substantial evidence that the drug will have the effect it purposes or is represented to have."
    - (7) Substantial evidence = randomized controlled clinical trials (RCT)

Truth Pursuant to the FFDCA



FDLI
Food and Drug Law Institute

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

"Promotional" Labeling

- Consistent with FDA-Required Labeling – CFL Guidance (Package Insert)
  - Medical Product Communications That Are Consistent With the FDA-Required Labeling — Questions and Answers Guidance for Industry (June 2018)
- Risk Information
  - Fair Balance
  - Prescriber and Consumer Brief Summary[1]
- Comparative Efficacy and Superiority Claims
- Clinically Meaningful Endpoints v. Surrogate (21 CFR 314.500-560 (1992))
  - Function or survival
  - Patient Reported Outcomes – Validation of Scale (*see also*, 21st Century Cures Act requiring patient input)
- Broadcast, Internet and Social Marketing
  - What is the Sponsor's role and influence?
  - Responsibility for correcting third party misinformation on company forum[2]
- Space Limitations: Twitter[3]

RCT Req'd

[1]21 CFR § 202.1(e) and Guidance (August 2015)
[2]Guidance on Internet/Social Media Platforms (June 2014)
[3]Guidance Advertising with Space Limitations (June 2014)

FDLI Food and Drug Law Institute

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

Summary

- A new drug is *a priori* misbranded or otherwise prohibited from introduction into commerce if the person responsible for the product makes promotional claims that do not reflect approved Package Insert (non-CFL).
- FDA's decision to approve is based on whether there are randomized controlled trials or evidence of comparable causal inference to support the proposed intended use, labeling, the conditions of intended use, the directions for use, and/or a claimed effect.

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

OTC Drugs I

- Memorandum of Understanding with FTC
  - FTC regulates advertising under a consumer confusion and false and misleading standard.
  - Consultation and/or referrals from FDA.
- Rx-to-OTC Switch
  - Existing new drug application with approved PI
  - Consumer labeling approved by FDA based on lay comprehension of intended use and safety
  - No fundamental change in FDA legal standards applicable to promotional labeling
    - An approved label

FDLI
Food and Drug Law Institute

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

OTC Drugs II

- Monograph products
  - Pre-1963 amendments non-prescription products
  - Drug Efficacy Study Implementation
  - NAS/NRC review: likely safe and effective (I); not likely safe and effective (II); no data (III)
  - Advanced, Proposed (TFM), and Final Rulemaking addressing API, dose, and approved labeling
  - Monograph products have an "approved" label – same rules re promotional labeling.
- CARES Act of 2020 (Title III Subtitle F §§ 3851-3862) FDCA § 505G on non-final monographs
  - Exempts monograph process from rulemaking
  - Finalizes all pending TFMs
  - Unfinished Category II products require a New Drug Application
  - Requests for changes and 18 month exclusivity – how enforced?
- Pre-1938 or pre-1962 identical, related or similar (IRS) (CPG 440.100) – not "new drugs"
  - Not Subject to Monograph
  - E.g., Ludens® cough drops, Donnatal®
  - FDA position is that any change in labeling or promotional claims renders the product a new drug subject to requirements for a New Drug Application

FDLI
Food and Drug Law Institute

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

Special Cases

- Securities and Exchange Commission & Patent and Trademark Office
- Pre-approval promotion – touting an investigational product that is not for sale[1]
- Health care economic information, e.g., payor communications[2]
  - Disease outcomes research, e.g., burden of disease, length of stay
  - Patient reported outcomes
  - Must be related to an approved indication
- No drug mentioned or drug mentioned but no claims
  - Disease specific if drug product is not mentioned[3]
  - Help seeking or reminder ads[3]
    - Only the drug name is included
  - Reminder advertising re pricing[4]

[1] Warning letters – Phoenix Imaging (2019); Arog (2018); UCLA (2017). More recently, opioid
[2] FDCA § 502(a)(1); Guidance for Industry on Payor Communications
[3] 21 CFR 201.100(f)
[4] 21 CFR § 200.200

FDLI
Food and Drug Law Institute

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

Office of Prescription Drug Promotion (OPDP)

- 21 CFR § 314.81(b)(3)(i) – "Other" reporting
  - At the time of initial dissemination
- FDCA § 745A(a) – Electronic format only (Form 2253)
- Office of Prescription Drug Promotion Submissions
  - Submission of all promotional materials is required
  - Review of "core" launch materials and advice requests
- Submission of Interactive Promotional Media[1]
  - Original static website, interactive components and monthly updates

[1]Guidance Fulfilling Requirements for Interactive Media (January 2014)

FDLI Food and Drug Law Institute

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

OPDP/APLB Enforcement

- What is reviewed?
  - Complaints – healthcare professionals, consumers, other sponsors, law firms and whistleblowers
  - BadAd@fda.gov
- Phone calls, emails, letters of inquiry
- Post-Marketing Letters (Untitled/Warning)
  - NB. Instructive to review “cosmetic” letters
- Corrective Actions
- Misbranding Charges
- Referral to Department of Justice
  - Anti-Kickback Law
  - False Claims Act
- Compliance Integrity Agreements

FDLI
Food and Drug Law Institute

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

Anti-Kickback

- Medicare and Medicaid
  - 42 U.S.C. § 1320a-7b(b)
- Prohibit a drug manufacturer from offering any remuneration to induce that a healthcare provider to offer or recommend any item or service which is paid by a Federal health care program.
- "Induce" is interpreted to mean that there are now "excess" payments by the government due to false or misleading claims that advocate use that is not approved.
- Penalty is disgorgement or refund.
- Healthcare provider engagements must be strictly monitored

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

Compliance Integrity Programs

- Code of Conduct
  - PhRMA Ethics Code[1]
- Clinical, Medical, Legal, Regulatory Review (CMLR)
- Compliance Subcommittee
- Chief Compliance Officer Oversight
  - Sales personnel monitoring
  - Sales personnel compensation
  - Speaker decks
  - Audit
  - Reports
  - Corrective actions
- Healthcare Provider (HCP) Engagement
  - Investigator initiated studies
  - Charitable contributions and grants
  - Continuing Medical Education
  - Dissemination of scientific and medical literature
- Self-reporting (Yates Memo)

FDLI
Food and Drug Law Institute

[1]https://www.phrma.org/en/Codes-and-guidelines

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

False Claims Act

- Can be brought by a relator or private party on behalf of the Government
- Fraudulent sale to the US Gov't
  - False Statement or course of conduct
  - Scienter
  - Material
  - Government in fact paid moneys
- Disgorgement

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

State and Private Enforcement

- Did the off-label promotion harm competitors?
  - Lanham Act and state unfair competition laws
  - Different standard for false and misleading
    - By a judge and/or jury
  - Proof of economic harm
- Consumer confusion
  - State consumer confusion laws and private rights of action
  - Not generally useful for Prescription Drugs
  - NB. Product liability can be based on failure to warn . . .

FDLI
Food and Drug Law Institute

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

Problems Emerge

- Is there a right to know?
  - Sponsors have comprehensive disease and drug information.
  - Doctors have limited time to read journals (Kefauver to present).
  - Consumers do not always know that there is a treatment available.
- Economic studies in other markets show clear consumer benefits to advertising – lower prices, better decisions, more informed of options.[1]
- But, launch of intensive marketing campaigns increases drug sales
  - Does the expanded usage result in unsafe or ineffective usage?
  - Is the pharmaceutical market different from others?
  - Temple Affidavit (Allergan 2007) and FDA Memorandum (January 2017)

[1]Nobel Prize -- George Stigler (1982) for demonstrating the economic benefits of advertising

FDLI Food and Drug Law Institute

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

Continuing Medical Education (CME)

- A form of remuneration that may include off-label information
- FDA Initiative in 1990s
  - 1997 Guidance
- ACCME and AMA Empowered
- Guidance – Criteria to "Factors"
  - Independence, control of content, selection of speakers
  - Disclosure of support
  - Nonpromotional focus

- Sponsor can influence provider vi relationship
- Sponsor access to audience
- Repeated
- Focus
- Prior failure
- Audience selection
- Opportunity for discussion
- Dissemination
- Ancillary promotional activities
- Complaint handlings
- Resort?

FDLI
Food and Drug Law Institute

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

Other Requests for Funding or Information

- Pharmaceutical firms largely underwrite professional meetings
  - How is promotion controlled?
    - Exhibit floor
    - Exhibit booth restrictions
    - Sales personnel training
    - Medical science liaison
- Medical Science Liaison
  - Unsolicited requests from healthcare providers
  - Guidance: Responding to Unsolicited[1] Requests (December 2011)
  - Scientific, truthful, nonmisleading, balanced, maintain records
- Request Reprints
- Each of these are forms of “remuneration” that could include off-label information

FDLI
Food and Drug Law Institute

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

Setting the Stage – Central Hudson

1. **Lawful and not misleading speech? (No – restriction OK)**
   - Yes: protected by 1st Amend., move on to part 2.
2. **Gov't interest served by restriction substantial? (No – restriction not permitted)**
   - Yes: move on to part 3.
3. **Restriction directly advances gov't interest? (No – restriction not permitted)**
   - Yes: move on to part 4.
4. **Restriction not more extensive than necessary to meet interest? (No, government cannot restrict)**
   - Yes: Gov't **can** restrict.

See also, Sorrell v IMS Health, 113 S. Ct. 2653 (2011) (heightened scrutiny if speaker and content based)

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

Washington Legal Foundation v. Henney

- 1962 to 1996
- FDA Guidances on Dissemination of Reprints/Reference Texts (1997)
- Found unconstitutional prior restraint WLF v. Henney (No. 94cv01306)
- FDAMA 1997 (Procedures for distribution of off-label information)
  - FDCA § 551-557 with 2006 Sunset
  - FDA Regulations 21 CFR Part 99
- Vacated on appeal as moot (202 F.3d 331)

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

Aftermath

- New Guidance (2000) – Safe Harbor
- FDAMA Sunset (2006) (21 CFR Part 99 effectively repealed)
- New Guidance (2009) – Off-Label dissemination may convey "intent"
- Latest Guidance (February 2014)

- Peer-reviewed
- Unabridged
- Well-designed
- Complete Labeling
- With bibliography
- With contrary publications or information when known
- Otherwise generally available
- Affixed with warning
- Unaccompanied by promotional literature other than labeling
- Not a supplement, marked or highlighted, influenced, funded

FDLI
Food and Drug Law Institute

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

US v Caronia, 703 F.3d 149 (2nd Circuit 2012)

- Sales rep convicted of conspiracy to introduce misbranded drug
  - "We agree" that Caronia "was convicted for his speech – for promoting an FDA-approved drug for off-label use – in violation of his right of free speech under the First Amendment."
  - Off-label statement can be evidence of intent for off-label distribution but cannot of itself be violative as protected speech.
  - Vacated and remanded for new trial
- Dicta (citing Liquormart v. Rhode Island, 517 US at 503, 1996)
  - "The First Amendment directs us to be especially skeptical of regulations that seek to keep people in the dark for what the government perceives to be their own good."

FDLI
Food and Drug Law Institute

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

Amarin Pharma v US, 119 F. Supp. 196 (SD NY 2015)

- Vascepa® (omega-3-fatty acids) approved for severe hypertriglyceridemia (≥500 mg/dL)
  - "Supportive but not conclusive research that . . . may reduce risk . . . in patients with high (≥200 mg/dL) triglyceride levels"
- Truthful and non-misleading statements
  - RCT study met standard for substantial evidence (ANCHOR Study)
  - But, FDA revised standard for "clinically-meaningful"
- Failed Central Hudson – injunction issued against FDA
  - Settled and limited advertising permitted (2016)
- REDUCE-IT completed September 2018
- sNDA submitted March 28, 2019
  - Approved for secondary prevention (≥150 mg/dL) (December 13, 2019)

FDLI Food and Drug Law Institute

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

US v. Vascular Solutions (WD Texas 2016)

- Laser device approved for superficial but not perforating varicose veins
- Citing Amarin and Caronia, Judge Lamberth's instructions to jury stated:

  Doctors may use medical devices that have been approved or cleared for one use for a different use that has not been cleared or approved by the FDA. This is often referred to as unapproved use or off-label use. This is not illegal. It is also not a crime for a device company or its representatives to give doctors wholly truthful and non-misleading information about the unapproved use of a device. If you find that VSI's promotional speech to doctors was solely truthful and not misleading, then you must find the Defendants not guilty of the misbranding offense.

- Jury found company and CEO not guilty of all charges

FDLI
Food and Drug Law Institute

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

FDA Memorandum (January 17, 2017)

- FDA Memorandum (January 18, 2017) Rationale for Agency Position
  - Robust Scientific Data on Safety and Effectiveness
  - Prevention of Fraud, Misrepresentation and Bias
  - Diversion of Health Care Resources to Unproven Therapy
  - Accuracy, Integrity, and Reliability of Labeling and Promotional Information
  - Informed Consent
  - Protecting Innovation and Promoting Sound Product Development
- Guidance Q&A on Medical Product Communications (June 2018)
  - How to determine whether information is definitively within labeling

FDLI
Food and Drug Law Institute

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

FDA's Post-2017 Approach

- Stop sending Warning Letters that reflect lack of support for claims to intended use.
- Focus on absent risk information and lack of fair balance
- And, for 2020, focus on COVID-19

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

False Claims Act Redux

- Recall tie of promotion to excess claims
  - Requires a demonstration of the materiality of the off-label promotion to government's payment of the excess claim.
  - Penalties more significant than those in the FDCA.
  - Would the government have bought if the government knew?
    - Off-label use by physicians is common and permissible.
- *Escobar v US*, 136 S. Ct. 1989 (2016)
  - "The materiality standard is demanding"[1]
    - Specific representation that is material to payment
    - Failure to disclose a material requirement
- Evolving case law that off-label promotion may not be material
  - But, issue is dismissal on the complaint[1]

[1]Escobar at 2003; *see* Genentech, 855 F.3d 481 (3d Cir 2017); Stephens Institute, 901 F.3d 1124 (9th Cir 2018); Moody's Corp, 2017 WL 825478 (SDNY 2017); Dr. Reddy's, 2017 WL 1133956; *but see* Gilead, 862 F.3d 890 (9th Cir 2017).

Jur Strobos
Potomac Law Group
jstrobos@potomaclaw.com

Summary

- Promotional labeling must conform to approved label.
  - Automatically misbranded
  - Substantial penalties through FDCA, Medicare/Medicaid laws and False Claims Act
- Compliance Integrity Programs
  - Oversight of marketing materials and HCP engagement
- Emerging weaknesses in FDA's case
  - First Amendment and "right to know"
  - Materiality limitation in *Escobar*