

Identifying Problematic Claims in Your (and Your Competitor's) Drug and Device Advertising

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Why Does It Matter?

- ▶ Costs associated with failure to comply:
 - ▶ Loss of customer confidence
 - ▶ Loss of government confidence
 - ▶ Expense of fines/lawsuits/enforcement
 - ▶ Potential effect on stock price

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Who Cares?

- ▶ Promotional communications will receive scrutiny in today's environment from:
 - ▶ FDA/FTC
 - ▶ Competitors
 - ▶ HHS/Private Payors
 - ▶ Media
- ▶ Increased expectations of transparency
 - ▶ Government, media, consumer watchdogs expect more transparency in dealings with physicians and consumers

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Report Misleading Rx Drug Promotion

The prescriber can play an important role in ensuring that prescription drug advertising and promotion is truthful by recognizing and reporting misleading drug advertising and promotion.

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Reporting Misleading Drug Advertising and Promotion

Prescription drug advertising must:

- Be accurate
- Balance the risk and benefit information
- Be consistent with the prescribing information approved by FDA
- Only include information that is supported by strong evidence

What types of promotion does the Office of Prescription Drug Promotion (OPDP) regulate?

- Sales representative presentations
- Speaker program presentations
- TV and radio advertisements
- All written or printed drug promotional materials

OPDP does not regulate promotion of:

- Over-the-counter drugs
- Dietary Supplements
- Medical Devices

Common Violations

- Downplaying or downstaging of risk
- Overstating the effectiveness
- Promoting off-label or unapproved uses
- Misleading drug comparisons

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Survey of Letters from FDA

Between October 2012 and September 2013 - 19 letters

18 untitled and 1 warning; and an unknown # of "letters of inquiry"

Topics:

- Risk information presentations (13)
- Data from flawed study designs unable to provide substantial evidence for claim (11)
 - Overstatement of efficacy
 - Unsubstantiated superiority
- Investigational product promotion (3)
- Press/news releases (3)
- Composite data (1)

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CDRH - Oversight of Device Ad/Promo

FDA Oversight of Advertising and Promotion

Effective November 2013, Office of Compliance reorganized

Division for Pre-Market and Labeling Compliance

- Will devote more time to monitoring device advertising and promotion and pre-market approval compliance
- Will be "more intentional" in oversight
- Will increase headcount devoted to monitoring (from 1 to 3 persons)

Doesn't require submission of device promo/ads prior to 1st use

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CDER - Oversight of Rx Drug Ad/Promo

Center for Drug Evaluation & Research

➤ Office of Medical Policy

➤ Office of Prescription Drug Promotion (OPDP) - Tom Abrams, Director

Mission

"To protect the public health by assuring prescription drug information is truthful, balanced and accurately communicated. This is accomplished through a comprehensive surveillance, enforcement and education program, and by fostering better communication of labeling and promotional information to both healthcare professionals and consumers."

➤ OPDP divided into 2 divisions - review both HCP and DTC materials (over 65 people)

Division I

Team 1 - Neurology, Psychiatry
Team 2 - Hematology/Oncology (blood cancers)
Team 3 - Oncology (solid tumors)
Team 4 - Analgesics, Anesthetics, Antivirals

Division II

Team 5 - Osteoporosis, Reproductive, Urology
Team 6 - Dental, Dermatology, Metabolic & Endocrine
Team 7 - Allergy, Gastroenterology, Pulmonary, Rheumatology
Team 8 - Anti-Infective, Cardiovascular, Medical Imaging, Ophthalmology, Renal Transplant

FDCA - Definitions

- "Label" – on immediate container of drug/device
- "Labeling" – labels and other written, printed or graphic material on drug/device, container, wrapper or "accompanying" the drug/device, (e.g., package insert or instructions for use)
- "Advertising" – understood to be:
 - Ads in journals, magazines, newspapers
 - Broadcast ads on TV, radio, telephone
- "Promotional Labeling" – brochures, reprints, price lists, catalogs, promotional press releases and other materials used in promotion

Note: FDCA treats advertising and promotional labeling differently

FDCA - Definitions

➤ "Restricted Devices"

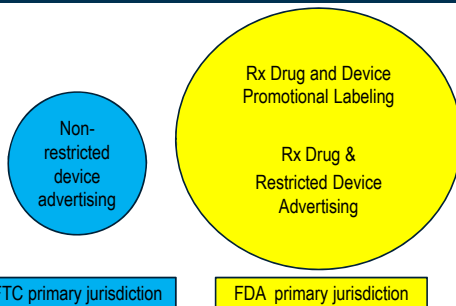
Devices may become restricted as part of pre-market approval (PMA), by regulation issued under FDCA or as part of an FDA performance standard.

- Most Class III devices are restricted and a few Class I and II (e.g. hearing aids)
- Prescription devices may or may not be restricted devices.

Regulation - Basics

- ▶ FDA vs. FTC jurisdiction
 - ▶ FDA has primary jurisdiction for labeling of FDA-regulated products (this includes promotional labeling of non-restricted devices)
 - ▶ Promotion on the internet is promotional labeling not advertising
 - ▶ FDA has primary jurisdiction for advertising of Rx drugs and restricted devices only
 - ▶ FTC has primary jurisdiction for advertising of other FDA-regulated products (including advertising of non-restricted devices)
- ▶ FDA/FTC will issue joint enforcement letters (e.g., food and dietary supplement health claims)

FDA vs. FTC Primary Jurisdiction for Rx Drugs and Devices



Regulation - Basics

- ▶ Independent health care professionals (HCP) can prescribe or administer drugs or devices for off-label use BUT...
 - ▶ FDA has recently issued warning letters for off-label promotion of FDA-regulated articles by medical clinics (Lasik, LapBand)
- ▶ Manufacturers may not:
 - ▶ Promote or test market a drug or device until after FDA has approved the product for commercial distribution
 - ▶ Represent that a drug or device is safe or effective for a purpose for which it is being investigated
- ▶ Violating this provision could result in significant civil and criminal penalties



What is Promotion?

- What is "promotion" subject to FDA regulation? (Not defined in the FDCA)
 - Information provided by or on behalf of a manufacturer about its products (written or oral)
 - FDA's position seems to be: All information from a manufacturer is promotion unless it is legitimate scientific exchange
- Companies should view as promotion anything that:
 - Contains a claim or representation about an existing or proposed company product made or used by any employee of the company (or agents, consultants, distributors or other 3rd parties working on behalf of the company) in connection with marketing, promotion or sales activities.
- Claims can be explicit or implicit

Promotional Communications - Examples

- ▶ Examples of Promotional Communications
 - ▶ Traditional promotional materials
 - ▶ Tradeshow displays/materials
 - ▶ Promotional press releases and media information kits
 - ▶ Handouts and slides used in presentations to advocacy groups/ company investors
 - ▶ Statements made or shown by promotional speakers
 - ▶ Journal or other scientific materials used in promotion
- ▶ Promotional materials should be reviewed for compliance with FDCA and other legal issues including:
 - Product liability, fraud & abuse, IP, competitor claims, SEC regulations

Promotional Communications - Criteria

- ▶ Promotional Communications must meet the following criteria, which are based upon the FDCA:
 - ▶ Be clear, accurate and truthful
 - ▶ Not be misleading (e.g., unsupported superiority claims or testimonials)
 - ▶ Promote only cleared or approved intended use (on-label)
 - ▶ Be supported by valid scientific evidence
 - ▶ Include a fair balance between benefits and risks
 - ▶ Draft "Guidance for Industry: Presenting Risk Information in Prescription Drug and Medical Device Promotion" (5/2009)
 - ▶ Applies to all media (print, TV, internet, Twitter, etc.), all audiences (HCP, payors, consumers) and equally to drugs and devices
 - ▶ Key concept: "Net Impression"

Promotional Communications – Not Misleading

- ▶ Not misleading
 - ▶ Claims can be misleading based upon representation, suggestion or omission
 - ▶ Misleading claims include:
 - ▶ Claims that lack required support
 - ▶ Data that is outdated/superseded
 - ▶ Graphics that are misleading
 - ▶ Results/quotations taken out of context
 - ▶ Data that has been "cherry picked"
 - ▶ Inaccurate or misleading information about a competitor's drug

Promotional Communications - Substantiated

- ▶ What constitutes adequate support for a claim?
 - ▶ Case-by-case analysis
 - Most conservative position:
 - ▶ For drugs – claims must be come from data in package insert (data "approved" by FDA)
 - ▶ For devices - if clinical claim, consistent with pre-market submission

Promotional Communications - Substantiated

- ▶ FTC Standards for non-restricted device advertising (and health, safety and product efficacy claims for other products subject to FTC jurisdiction)
 - ▶ "Competent and reliable scientific evidence"
 - ▶ Case-by-case analysis
 - ▶ Generally, "tests, analyses, research, studies or other evidence based on the expertise of professionals in the relevant area, that has been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the profession to yield accurate and reliable results."

Comparative Claims - Background

- ▶ Comparative claims are risky
 - ▶ Claims of equivalence or superiority
 - ▶ These include words like "unsurpassed," "similar to," "equivalent," "gold standard," "most," "only," "greater, greatest, quicker, quickest, better, best," etc.
 - ▶ Comparative claims must be truthful and non-misleading
 - ▶ Is the comparison clinically relevant?
 - ▶ Is it consistent with approved indications for use of device/drug being compared?
 - ▶ Is the comparison a scientifically valid one and presented in a fair and transparent manner?
 - ▶ **NOTE:** You can misbrand your device/drug by making a false or misleading representation about another device, drug or cosmetic (21 CFR 801.6, CFR 202.1(3)(6)(iii))

Comparative Claims - Substantiation

- ▶ What data is required for a comparative claim?
 - ▶ Comparison as to clinical safety/effectiveness
 - ▶ "Substantial evidence"
 - ▶ For Rx drugs: Typically 2 adequate and well controlled studies but FDA may accept 1 study with confirmatory evidence -21 USC § 355(d)
 - ▶ For devices: FDA enforcement has referred to head-to-head comparative studies
 - ▶ Other comparative claims (e.g., mechanical/material performance) related to health
 - ▶ "Competent and reliable scientific evidence"
 - ▶ Generally, direct testing or reliable references
 - ▶ Would a scientist be willing to testify as to superiority/equivalence?

Comparative Claims – Fair Comparisons

- ▶ Comparisons should be fair
- ▶ For example:
 - ▶ Cannot suggest product is superior simply based upon one-day dosing regimen; must have head-to-head trial demonstrating clinical superiority (untitled letter to Pfizer re: Zmax 6/19/12)
 - ▶ Unfair and misleading to imply general superiority of Focalin XR based upon the benefit demonstrated at two hours. Focalin is a biphasic release drug, and the competitor drug is an extended release drug (see untitled letter to Novartis re: Focalin XR 5/31/11)

Comparative Claims - Other issues

- ▶ OPDP has objected to clinical comparisons based upon:
 - Non-clinical data (in vitro/MOA/PK)
 - Post-hoc and meta analyses
 - Pooled analyses (combining individual studies)
 - Open-label studies
 - Observational studies
- ▶ Other considerations for devices:
 - ▶ If your device was cleared as substantially equivalent to a predicate device (510k), can it have superior safety or efficacy?
 - ▶ Often superiority claims reflect new intended uses requiring new 510k/PMA (e.g., change from general to specific use)

OPDP Comments re: Comparative Claims

- ▶ May 7, 2014, Federal Register announcement that FDA is researching how price comparisons may mislead consumers and physicians:
<http://www.gpo.gov/fdsys/pkg/FR-2014-05-07/pdf/2014-10410.pdf>
 - ▶ Focus: DTC advertising aimed at diabetes patients and physicians who treat diabetes
 - ▶ FDA concern is that patients assume products are interchangeable
 - ▶ If make price comparisons should note:
 - ▶ Drugs compared may not be comparable in terms of safety/efficacy
 - ▶ Acquisition price doesn't necessarily reflect actual prices paid
- ▶ OPDP considering guidance on prescription drug comparative claims

Endorsements and Testimonials

- ▶ Must be truthful and not misleading
 - ▶ Must reflect the honest opinions, findings, beliefs or experiences of the endorser
- ▶ Must clearly and conspicuously disclose the generally expected results, and advertiser must have adequate substantiation for claims being made
- ▶ Material connections between the endorser and the advertiser must be disclosed
- ▶ **Disclaimers will not correct an overall misleading impression**
 - ▶ "Results not typical" and "your results may vary" will not reduce the impression that the experiences depicted were typical

[FTC Guide Concerning Use of Endorsements and Testimonials in Advertising](#)

Lanham Act - Background

- ▶ Prohibits any use of a false or misleading description or representation in commercial advertising or promotion that "misrepresents the nature, characteristics, qualities, or geographic origin of... goods, services, or commercial activities."
- ▶ Pom Wonderful v. Coca-Cola Supreme Court decision - Lanham Act lawsuits are not precluded when a product regulated by FDA is involved
 - ▶ May result in expansion of competitors bringing Lanham Act claims against each other over false or misleading statements.

Example: Lanham Act Enforcement

Ferring Pharmaceuticals v. Watson Pharmaceuticals

- ▶ Watson, through a paid consultant, allegedly made statements that its vaginal progesterone gel produces more pregnancies and is safer and more convenient than Ferring's product.
 - ▶ Ferring requested a preliminary injunction to halt Watson's ads and compel corrective advertising; citing evidence that the statements made were untrue.
 - ▶ The district court and Third Circuit Court of Appeals denied Ferring's request for an preliminary injunction, finding that Ferring was not entitled to any presumption of irreparable harm because there was no evidence the false statements would continue.

Example: Lanham Act Enforcement

- ▶ Lanham Act suits can lead to additional ramifications, including further litigation:
 - ▶ After a federal court enjoined Pfizer's claim for mouthwash Listerine being "as effective as" dental floss in reducing the risk of gingivitis, consumer class actions were filed around the country, targeting the same advertising under state laws.
 - ▶ In Zeneca, Inc. v. Eli Lilly and Company, Lilly was found to have violated the Lanham Act by promoting its osteoporosis therapy Evista off label for the prevention of breast cancer. Several years later, Lilly faced a Department of Justice criminal investigation into the same conduct and ultimately pled guilty to a misdemeanor count of misbranding. Lilly agreed to pay the government \$36 million in fines, forfeiture and disgorgement

Consequences of Violations of FDCA

- ▶ Untitled or Warning Letter from FDA
 - ▶ Prosecution for more serious FDA violations
- ▶ Corrective Advertising
- ▶ Dear Doctor Letter
- ▶ Fallout, including lawsuits/enforcement
 - ▶ State/Federal False Claims Act
 - ▶ Product liability
 - ▶ FTC and State unfair & deceptive trade practice
 - ▶ Lanham Act
 - ▶ Private litigation (shareholder, product liability)

FDA Enforcement: Comparative Claim

- ▶ Merz Pharmaceuticals (Untitled letter, July 31, 2013) – Cited Rx drug comparative claims on webpage and banner ads re: Naftin cream
"Twice as Strong Half as Long"

FDA found promotion:

- Suggested Naftin was superior to other anti-fungal treatments based upon its 2-week treatment period

Other products also had a treatment period of 2 weeks (or less)

- Referred to "proven safety established from naftifine hydrochloride for over 20 years"

But Naftin had a different strength and dosage than the initial formulation

FDA Enforcement: Superiority Claim

- ▶ Baxter (Warning Letter, 2009) – Rx drug

Brochures and presentations for TISSEEL, a fibrin sealant product, claimed that "TISSEEL is the only sealant and hemostat in the U.S. containing aprotinin as an antifibrinolytic to preclude premature clot lysis....No competing fibrin sealant offers surgeons this combination."

FDA found these claims misleading because:

- ▶ the clinical significance of enhanced clotting characteristics of aprotinin and higher tensile strength of increased concentrations of human fibrinogen in TISSEEL had not been demonstrated; and
- ▶ they misleadingly implied superior clinical advantage over competing fibrin sealants *without comparative clinical data (substantial evidence) to support the claim*

FDA Enforcement: Comparative Claim

- ▶ Augustine Biomedical & Design - (Warning Letter, 2012) - Device 510k

Hot Dog Patient Warming System cleared to prevent or treat hypothermia and to provide warmth to patients in hospitals and surgical centers

Company website contained claims related to lower infection rates when using the air-free Hot Dog system as compared to forced-air systems

FDA indicated promotion for infection reduction is a major change or modification in the intended use of the device, **which requires submission of supporting clinical data and a new pre-market notification**

FDA Enforcement: Superiority Claim

- ▶ TherMatrix (Warning Letter, 2004) – Device- PMA

- ▶ FDA objected to:

- ▶ Off-label promotion

Brochure obtained by FDA at professional meeting claimed the product treated median lobe enlargement of the prostate when the product was approved only to treat certain category of men with benign prostatic hyperplasia (BPH)

- ▶ Unsubstantiated effectiveness claims

Made claims related to "proven 5 year durability" when PMA approval was based upon 1-year data. FDA asked for data to support the claim.

- ▶ Unsupported superiority claim

Made claims related to 'Superior Peak Flow Rate Improvement.' FDA stated it **would require data establishing statistically significant improvement over other therapies** (Note that no other products were specifically named)

FDA Enforcement: Implied Superiority Claims

- ▶ Curatronix Ltd. (Warning Letter, 2013) - 510k-Device cleared for stroke rehab and certain other uses. FDA stated:

"... comparative claims regarding the device being the best and easiest stroke rehabilitation system in the world **requires clinical data and a new 510(k) submission.**" Also, issue re: off-label claims (rehab after spinal cord injury and cerebral palsy)

- ▶ Note: did not compare its device to another specific device or general type of devices - just used superlatives "best and easiest"

- ▶ Pharmacia/Upjohn (Warning Letter, 2001) - contact lens brochure pictured two lenses side by side and noted Pharmacia/Upjohn lens did not have a square edge to inhibit posterior capsule opacification (PCO). FDA stated: "Although in most instances there are no explicit claims of superiority, the mere presentations of each lens's specifications constitute implied superiority claims." FDA stated that **"comparative claims in general are only appropriate if there are data resulting from head-to-head comparative studies."**

FDA Enforcement: Testimonial

► Teva (warning letter, 2012): Rx drug

Exhibit panels and website re: Copaxone, a drug treatment for MS

FDA stated:

- Misleadingly suggests that Copaxone is superior to other therapies and "misleadingly broaden the indication and overstate the efficacy of Copaxone by implying that Copaxone reverses patients' disability and enables them to lead an active lifestyle, return to work, accomplish great athletic feats "
- Includes numerous claims regarding the benefits of Copaxone, but fail to include any risk information associated with the drug in the body of the webpages (links to PI and safety information was inadequate)
- Disclaimers that "...individual results may vary" do not mitigate the misleading impression
- FDA required corrective messaging for the same duration of time and frequency that the violative promotional material was disseminated

FDA Enforcement: Testimonial

► Vertex (Untitled letter, 2012):

Incivek, Rx drug treatment for Hepatitis C

FDA stated that testimonial:

- Makes representations or suggestions that the drug is better or more effective **than demonstrated by substantial evidence or substantial clinical experience**
- Misleadingly suggests usual outcome of treatment with Incivek is a positive effect on a patient's interpersonal relationships, physical functioning, work productivity and overall quality of life.
- Minimizes the risk of rash and alopecia associated with Incivek combination therapy

Strategies for Challenging a Competitor Practice

1. Take a deep breath!
2. Make certain you want to launch the 1st bomb
3. Carefully evaluate the concern/allegation brought forward about the competitor
 - What is the "heart of the matter?"
 - Representative activity?
 - Promotional material?
 - Activity on the part of a consultant/speaker. If yes, is he/she contractually bound to follow your label/rules?
 - All of the above?
4. Gather all the relevant background/proof
5. Work with a cross-functional team to evaluate the concern/proof and determine if a complaint is warranted and strategic

Strategies for Challenging a Competitor Practice (cont.)

6. Consider whether raising the issue may subject your company to regulatory, legal, or policy risks (i.e., "glass house" issues)
7. Determine the best approach for raising the issue:
 - a) Informal contact between heads of Regulatory, Legal or company management;
 - b) Formal "cease and desist" letter; or
 - c) Notice to FDA and/or FTC

Important:

- Remember, any document created may later be used in litigation or a government enforcement action. Consider whether you need to consult with an attorney.
- If you call something out as illegal or impermissible, be sure you aren't doing it!

Strategies for Responding to Competitor Complaints

1. Take a deep breath!
2. Promptly acknowledge receipt of the complaint without commenting on its merits
3. Carefully evaluate the allegation.
 - ▶ What is the "heart of the matter?"
 - ▶ Representative activity?
 - ▶ Promotional material?
 - ▶ Activity on the part of a consultant/speaker. If yes, is he/she contractually bound to follow your label/rules?
 - ▶ All of the above?
 - ▶ None of the above?
4. Gather all the relevant background
5. Work with a cross-functional team to evaluate the claim and determine appropriate response

Strategies for Responding to Competitor Complaints (cont.)

6. Consider what regulatory, legal, policy issues the complaint may raise and who may need to be notified
7. Determine what type of response, if any, is warranted:
 - a) verbal (if no benefit to creating a paper trail);
 - b) paper only if want a paper trail and no need to explain/"personalize" response; or
 - c) both

Important:

- Avoid conclusive statements in your response. The company may later learn of facts and circumstances that change its characterization of an event
- Remember, this document may later be used in litigation or government enforcement action. Consider whether you need to consult with an attorney

Best Practices for Marketing Your Product

- ▶ Understand how your product is regulated
- ▶ Identify the nature of the communication, rules and control channels of communication
 - ▶ Promotion, scientific exchange, disease state education, etc.
- ▶ Create review processes & guidelines for employees
 - ▶ Use a multi-disciplinary review team
 - ▶ Develop clear policies and procedures
- ▶ Assume you must follow traditional rules
 - ▶ Truthful, on-label, fairly balanced, transparent as to sponsorship
- ▶ Be prepared for a mistake/crisis
 - ▶ Know how to respond to a government inquiry or 3rd party complaint

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