

**Regulatory Affairs Professionals Society:
Regulatory Affairs Certification (RAC) Study Group**

FDA Regulation of Advertising and Promotion

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Agenda

- FDA Regulatory Framework
- Office of Prescription Drug Promotion (OPDP)
- Promotional Review Committees (PRC)
- Examples of Violative Claims
- Electronic Advertising

FDA Regulatory Framework

FDA Regulatory Framework

- FDA issues regulations and guidance on content and format, including:
 - Statements on product uses and prescribing information
 - Brief summary relating to side effects, contraindications, and effectiveness (statement of Important Safety Information (ISI))
 - Instructions for use
 - Prominence of statements; clarity of messages

- FDA reviews product labeling, advertising, and promotional activity
 - Must not be “**false or misleading** in any particular”
 - FDA considers not only words or statements, but also designs and images, format and placement of text
 - Claims must be within the scope of approved labeling or within scope of marketing authorization or classification regulation – focus on **safety and efficacy** claims
 - Risks and benefits must be presented in a fair/balanced manner
 - Must contain material facts regarding consequences that may result from the use of the product under normal conditions

“Net Impression” and “False or Misleading”

- FDA guidance states that the agency evaluates the “**net impression**” of a promotional piece “to determine whether the piece **as a whole** conveys an **accurate** and **non-misleading** impression of the benefits and risks of the promoted product.”
- “promotional communication that conveys a **deceptive net impression** of the product could be misleading, even if specific individual claims or presentations are not misleading”
- “promotional pieces that fail to present a **balanced view** of the risks and benefits of a product are generally considered to be **false or misleading** and also generally fail to reveal **material facts** about the product being promoted”

Substantial Evidence

- For drug approval and promotion, safety and efficacy claims must be supported by “substantial evidence.”
- Substantial evidence generally means **two adequate and well-controlled studies.**
 - Food, Drug, and Cosmetic Act (FDCA) § 505(d)

Office of Prescription Drug Promotion

The Office of Prescription Drug Promotion (OPDP)

- Office within CDER that is responsible for reviewing prescription drug advertising and promotional labeling to ensure that they are not false or misleading.
 - As of September 2011, upgraded from the Division of Drug Marketing, Advertisement and Communication (DDMAC)

- Responsibilities include:
 - providing advisory comments to pharmaceutical sponsors on proposed promotional materials
 - reviewing complaints about alleged promotional violations (e.g., Bad Ad Program)
 - initiating enforcement actions on promotional materials that are false or misleading (e.g., Untitled/Warning Letters)
 - comparing the product labeling and promotional materials of various closely related products to ensure that the regulatory requirements are consistently and equitably applied
 - traveling to major medical meetings and pharmaceutical conventions to monitor promotional exhibits and activities

OPDP

- Types of promotion OPDP regulates:
 - TV and radio advertisements
 - All written or printed prescription drug promotional materials (includes the internet)
 - Speaker program presentations
 - Sales representative presentations

- Common Violations:
 - Omitting or downplaying of risk
 - Overstating the effectiveness
 - Promoting unapproved uses
 - Misleading drug comparisons (head-to-head studies required)

Form FDA-2253

- Sponsors “shall submit specimens of mailing pieces and any other labeling or advertising devised for promotion of the drug product **at the time of initial dissemination** of the labeling and at the time of initial publication of the advertisement for a prescription drug product.”
- “Each submission is required to be accompanied by a completed transmittal **Form FDA-2253** (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use).”
 - 21 CFR § 314.81
- Submission of a 2253 does **not** constitute OPDP pre-review and approval or qualify as seeking advisory comments.
 - Promotional pieces may be subject to an FDA enforcement action at any time, even **after** a sponsor has discontinued use.

Form FDA-2253

Form Approved: OMB No. 0910-0001, Expiration Date: September 30, 2014; see OMB Statement on Page 3.

TRANSMITTAL OF ADVERTISEMENTS AND PROMOTIONAL LABELING FOR DRUGS AND BIOLOGICS FOR HUMAN USE		1. DATE SUBMITTED	3. NDA/ANDA/AADA OR BLA/PLA/PMA	
		2. LABEL REVIEW NO. (Biologics)	Number: _____ Single product <input type="checkbox"/> Multiple products <input type="checkbox"/> For multiple products, submit completed form and specimen of advertising/promotional materials to one application of choice, and attach separate sheet addressing items 3-5 for remainder of products. Refer to No. 3 on instruction sheet.	
NOTE: Form 2253 is required by law. Reports are required for approved NDAs and ANDAs (21 CFR 314.81)				
4. PROPRIETARY NAME		5. ESTABLISHED NAME		
_____		_____ Prod. Code No. _____		
6. PACKAGE INSERT DATE and ID NO. (Latest final printed labeling)		7. MANUFACTURER NAME:		
_____		_____ License No. (Biologics) _____		
FDA/CBER USE ONLY				
REVIEWED BY	DATE	RETURNED BY	DATE	
_____	_____	_____	_____	
8. ADVERTISEMENT / PROMOTIONAL LABELING MATERIALS				
Please check only one: <input type="checkbox"/> Professional <input type="checkbox"/> Consumer				
Material Type (use FDA codes) a.	Dissemination/ Publication Date b.	Applicant's Material ID Code and/or description c.	Previous review No. if applicable / date (PLA Submissions) d.	COMMENTS:
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____

Bad Ad Program



- Program administered by OPDP to educate healthcare professionals on how to identify and report potentially false or misleading promotion
- Helps to address FDA's limited ability to observe drug promotion in settings such as physician offices, local dinner programs, and promotional speaker training sessions
- May lead to Untitled/Warning Letters or other enforcement actions

Promotional Review Committees

Promotional Review Committees (PRC)

- Purpose: Review all company promotional materials to ensure they comply with FDA regulations and other legal considerations
 - PRCs are not a legal requirement but most pharma companies use them because of the highly regulated nature of the industry.

- Comprised of members from:
 - Marketing
 - Medical Affairs
 - Legal
 - Regulatory Affairs

- The decision-maker may be Regulatory, Legal, or based on consensus, depending on the company.

PRC – Common Regulatory Affairs Responsibilities

- Fair balance and required safety disclosures (including accuracy)
- Ensuring claims are on-label
- Font size
- Disclaimers and limitations
- Knowledge of the product's label
- Knowledge of any relevant advisory comments from FDA
- Knowledge of relevant or recent FDA Warning/Untitled Letters and other enforcement actions
- Ensuring all PRC changes are pulled through in the final version
- Filing the 2253

Examples of Violative Claims

Off-Label Claims

- FDA takes the position that off-label promotion can create a new “intended use” for a drug, for which “adequate directions” are required under FDCA §502(f)(1), and cause a drug to be a “new drug” for which approval of an NDA is required under FDCA § 505(a)
 - The term “off-label” does not appear in the FDCA or FDA regulations.

- Examples of off-label uses include new indications, broadening of indications, and unapproved patient populations:
 - In 2012, GSK paid \$3 billion, the largest healthcare fraud settlement in U.S. history, regarding charges that included off-label promotion of the antidepressant, Paxil, for unapproved pediatric patients and off-label promotion of the antidepressant, Wellbutrin, for weight loss, the treatment of sexual dysfunction, substance addictions, and ADHD.
 - In 2008, FDA sent a Warning Letter to Bayer regarding the off-label promotion of Yaz for treating PMS and acne of all severities, when the drug was approved for treating premenstrual dysphoric disorder (PMDD) and moderate acne.

Implied Claims – 2012 Tarceva Untitled Letter



- “[B]ecause the Tarceva hourglass is positioned on its side, it appears that the sand in the upper half is no longer flowing down to the lower half where the cancer patient and child are located. This presentation **strongly suggests that time is standing still for the cancer patient** because of Tarceva therapy. This suggestion **drastically overstates** the overall survival benefit for patients.”

Comparative/Superiority Claims – 2012 Zmax Untitled Letter

If the whole therapy is just 1 dose, will I or my child get better faster?

Like all antibiotics, *Zmax* does take time to work. Most kids begin to feel good in just 2 to 3 days. If symptoms are not better by Day 4, call your doctor.

Will my child be able to handle a medicine with just one strong dose?

Zmax is different from other drugs, because it's not released in the stomach. *Zmax* goes to work in the small intestine so it's easier on the stomach. Unlike many other drugs, you should take *Zmax* on an empty stomach.

My child always complains about

“The above claims are misleading because they imply that *Zmax* demonstrates a superior safety profile when compared to other antibiotics, due to the supposed superior tolerability of the drug. FDA is not aware of adequate and well-controlled **head-to-head studies** to support this implication.”

“The totality of these claims misleadingly suggests that *Zmax* is clinically superior to other antibiotics because of its ‘1 day, 1 dose’ dosage regimen.... claims of superiority must be supported by adequate and well-controlled **head-to-head clinical trials** comparing appropriate doses and dose regimens of your drug and the comparator drug or drugs.”

 patients were cured

What are the benefits of an antibiotic that is given as a 1 day, 1 dose?

For Adults: If you are sick, a 1-dose option makes treatment easier on you.

- Your body gets more medicine on Day 1 when it needs it most
- No need to worry about missing a dose

For Children: It can be tough to give your child medicine but treating with *Zmax* means:

- 1 dose and your child is done with treatment
- No need to keep track of multiple day doses

The most common side effects in adults are diarrhea/loose stools, nausea, stomach pain, headache, and vomiting.

The most common side effects in children are vomiting, diarrhea/loose stools, nausea, and stomach pain.



Non-Representative Claims – 2012 Ampyra Untitled Letter



- “Bonnie Leedy talks about her experience with Ampyra while **images of her snowboarding and horseback riding** are shown. The **totality** of the above claims, along with these images, **misleadingly** suggests that treatment with Ampyra can have a positive impact on the disability caused by MS such that patients can carry out daily activities that they may not have chosen to do before because of difficulty in walking.”

Disclaimers – 2012 Firmagon Untitled Letter

From
Firmagon's
Prescribing
Information

In the clinical trial, PSA levels were monitored as a secondary endpoint. PSA levels were lowered by 64% two weeks after administration of TRADENAME, 85% after one month, 95% after three months, and remained suppressed throughout the one year of treatment. These PSA results should be interpreted with caution because of the heterogeneity of the patient population studied. No evidence has shown that the rapidity of PSA decline is related to a clinical benefit.

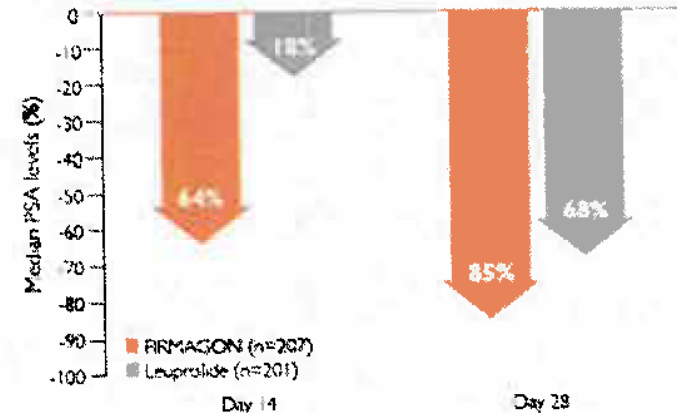
From
Firmagon's
Sales Aid

FIRMAGON
REDUCES PSA LEVELS
BY MORE THAN
60%
IN JUST 2 WEEKS²

Provides rapid and sustained reduction in PSA²

- In 2 weeks, FIRMAGON reduced PSA levels by 64%²
- Patients treated with LHRH agonists experienced an 18% overall reduction in 2 weeks²

Rapid PSA reduction:



These PSA results should be interpreted with caution because of the heterogeneity of the patient population studied; no evidence has shown that the rapidity of PSA decline is related to a clinical benefit.

Disclaimers

- OPDP found these claims to be misleading despite the fact that the **data was reported in the clinical studies section** of Firmagon's PI and despite the fact that the sales aid **contained the same disclosure that appears in the PI.**
- “This presentation misleadingly suggests that the velocity of PSA reduction is clinically meaningful for patients with advanced prostate cancer when this **has not been demonstrated by substantial evidence** or substantial clinical experience. We note the statement, ‘These PSA results should be interpreted with caution because of the heterogeneity of the patient population studied; no evidence has shown that the rapidity of PSA decline is related to a clinical benefit,’ appears below the graph on page six; **however, this statement does not mitigate the misleading impression conveyed by the claims included in the sales aid.**”

Other Common Issues

- Subgroup claims without supporting substantial evidence
- Retrospective or post-hoc data analysis based on non-pre-specified time points
- Use of survey results, which does not constitute substantial evidence

Electronic Advertising

Internet Advertising

■ Sponsored Links

- In 2009, FDA sent Untitled Letters to 14 pharmaceutical companies regarding sponsored links for prescription drugs on internet search engines.
- The links misleadingly “fail[ed] to communicate **any** risk information.”
- FDA concluded that the inclusion of links to the product websites – the so-called “one-click” rule – was “insufficient to mitigate the misleading omission of risk information.”

YAZ® Birth Control Pill

www.Yaz-US.com YAZ® Prevents Pregnancy, May Help Moderate Acne and PMDD.

Internet Advertising

■ Web Banners

- In 2009, FDA issued an Untitled Letter for Treximet regarding web banners that misleadingly “minimize[d] serious risks and inadequately communicate[d]” material facts.
- Specifically, risk information was presented in a small, scrolling portion of the banner that was “almost impossible to read” because of the fast automatic scrolling speed and small text size.
- In addition, there was no signal to alert consumers that the text contained important risk information.
- Although this letter applied to a black box drug, FDA may evaluate in-banner disclosures for all drugs in a similar fashion.

Internet Advertising

- Key Takeaways
 - The nature of internet linking does not negate a company's duty to still adequately disclose risks.
 - Risk disclosure must be meaningful – not just present – even in web banners.

Social Media

- The requirements for social media are unclear because there are no FDA regulations or guidance that specifically address social media.
- By statute, FDA is required to issue guidance by July 2014 on internet promotion, including the use of social media.
 - Food and Drug Administration Safety and Innovation Act § 1121

Social Media

■ Facebook and Twitter

- In a 2012 Warning Letter to Amarc Enterprises regarding the marketing of a dietary supplement as a drug on a company Facebook page, FDA cited:
 - A user's post "liked" by the company in which the user endorsed the product as an effective cancer treatment
 - A company post that provided a link to a blog post which in turn contained a cancer treatment claim and a link to a third party website regarding cancer treatment.
- In a 2012 Warning Letter to Vitality Distributing regarding the marketing of caffeinated water as a drug on company Facebook and Twitter pages, FDA cited:
 - Company posts that provided a link to an article that contained depression, cancer, and Alzheimer's treatment claims for caffeinated coffee.

Social Media

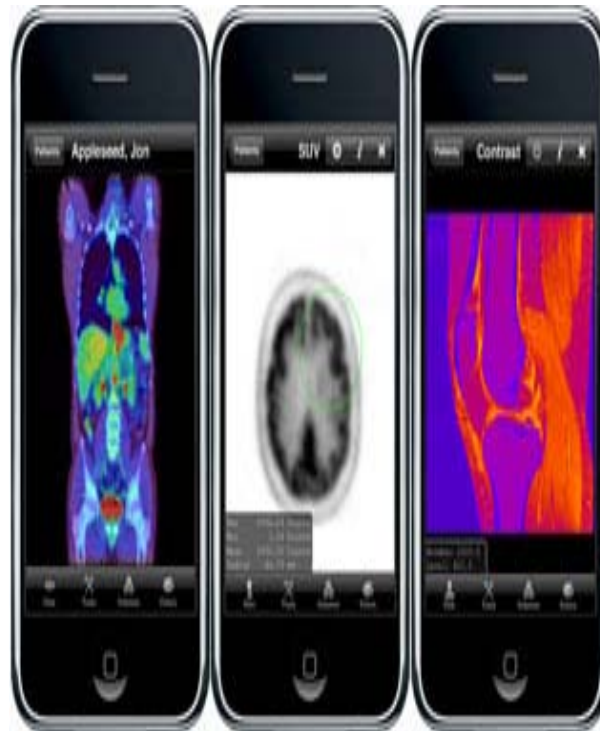
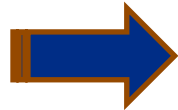
■ Key Takeaways

- Companies cannot use third parties to promote claims that they themselves could not otherwise make.
- FDA will likely scrutinize everything a company links to for product claims (direct or implied), including:
 - Further linked materials from those original links
 - Content that does not even directly relate to the product
- If companies choose to use social media, they must be vigilant about monitoring, and there will always be risk given the uncontrolled nature of the content.

Mobile Medical Applications (MMAs) are Medical Devices

- According to FDA draft guidance, a **mobile medical application (MMA)** is “a mobile app that meets the definition of a ‘device’ in section 201(h) of the [FDCA] and either:
 - Is used as an accessory to a regulated medical device; or
 - Transforms a mobile platform into a regulated medical device.”
- This may include apps that allow healthcare providers to view MRIs or other medical images on a mobile platform; analyze or interpret medical data (e.g., electrocardiograms); or monitor vital signs and other physiological information through a mobile platform (e.g., blood glucometers).
- However, this does **not** include mobile reference materials and textbooks; systems used solely to log, record, or make suggestions related to general health and wellness (e.g., dietary tracking logs); automated general office operations and electronic health records; and general personal aids (e.g., apps that use the mobile platform as a magnifying glass).

FDA Software/Health IT Issues in Practice: MiMVista and FDA



FDA Software/Health IT Issues in Practice: MiMVista

(cont'd)

- Mobile MIM is a free app that displays full-resolution medical images (e.g., CT and MRI)
- Won Apple Design Award for Best iPhone Healthcare & Fitness Application (2008)
- First introduced at the launch of the App Store
- A few weeks later, FDA asked the company to remove the app from the App Store and MiMVista promptly removed it
- August 2008: Developer submitted 510(k) seeking FDA marketing clearance

FDA Software/Health IT Issues in Practice: MiMVista

(cont'd)

- June 2009: Second 510(k) submitted and subsequently not cleared; FDA concluded that:
 - Medical images for diagnostic use on a mobile device is a new intended use of existing diagnostic devices
 - Device has a new indication for displaying medical images for diagnostic use and changes the effect, safety and effectiveness
 - There was not currently marketed device with the same functionality to which the MIM device could be compared for safety (i.e., no “predicate” device to which the MIM could be found to be “substantially equivalent”
 - As a result, the device was automatically classified as a Class III Device, and subject to the more stringent premarket review requirements for class III devices

- FDA cleared the device in February 2011
 - Indication is limited to use only when there is no access to a full viewer workstation and not intended as a replacement for a full workstation
 - May not be used for mammography

MMA's

- Key Takeaways
 - If launching a mobile app (or new functionalities to an existing mobile app), companies should carefully analyze whether FDA will regulate it as a medical device.
 - A mobile app may be required to comply with medical device regulations as well as general advertising and promotion regulations.

Overall Key Takeaways

- Because the pharmaceutical industry is highly regulated, companies must carefully review all promotional materials prior to dissemination.
- Regulatory Affairs plays a central role in knowing the regulations and identifying key issues.
- The “false or misleading,” “net impression,” and “substantial evidence” standards should form the basis for all of your promotional review decisions.
- Until FDA provides further guidance, electronic advertising presents risks due to an uncertain regulatory framework and the uncontrolled nature of social media.