Advertising and Promoting In Vitro Diagnostics

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Overview

- Every device company – including IVD manufacturers – needs to promote its products
- The Federal Food, Drug, and Cosmetic Act (FDCA) limits the manner in which products can be promoted
- The goal: communicating fully and accurately within the constraints of the law
- What is the law isn't always clear
- FDA enforcement has increased significantly in the past few years
  - More large settlements, more investigations, and more warning letters

Intended Use

- A key regulatory concept
- The regulatory classification may hinge on the intended use of the product, not what it does
- Intended use is governed by the objective intent of the manufacturer – 21 C.F.R. § 801.4
- This objective intent is set forth in the words and images communicated by the company and its agents
  - Essentially any communication by the company or its employees can be cited by FDA to determine intended use
- Intended use – at least historically – is not determined by how the product is actually used

Intended Use (cont'd)

- Communications by the company or its employees can change the intended use
- Promoting the product for a new intended use can mean that an exempt product needs a 510(k) ("trip the limits of the exemption"), or a 510(k) product needs a new 510(k) or a PMA
- Intended uses are generally very specific, e.g., aid in diagnosing, and in diagnosing, monitoring, prognosis, etc.

Intended Use (cont'd)

- Intended use can be based on oral statements by employees or agents, such as
  - Sales calls
  - Site training
  - Trade shows or meetings, e.g., AACC
  - Speeches by sales reps
- Intended use can be affected by statements by third parties, e.g., testimonials, that are referenced or used by or on behalf of the manufacturer

Intended Use (cont'd)

- The regulatory classification of a product may vary as a function of the claims
- Example: Mass spectrometer
  - When intended for use as a research tool, a Research Use Only (RUO) product
  - When intended for clinical use but no specific medical claims, i.e., "to identify inorganic or organic compounds . . . in human specimens," a Class I device subject to QSRs. 21 C.F.R. § 862.2860
  - When intended for neonatal screening, Class II
  - When intended for ovarian cancer screening, Class III
  - If no clinical claims at all, arguably not subject to FDA regulation

Labeling

- Labeling includes the label and other written or graphic materials “on or accompanying” the device
- Labeling encompasses all written materials physically accompanying the product
- Labeling also includes written materials that are not distributed with the product, but relate directly to it, e.g., part of a coordinated program to convey information about the product

Labeling (cont'd)

- Examples include
  - Brochures
  - Instructions for use
  - Manuals
  - Training slides for laboratories
  - Slide decks prepared for physicians
- FDA can use labeling to discern intended use
- If intended use deviates from cleared or approved use, then there can be a regulatory violation

Labeling (cont'd)

- Labeling can be violative even if no new intended use
- False or misleading statements in labeling render the device misbranded
  - "Misleading" can be based on omissions or visual imagery
  - A statement can be literally true but misleading
  - Statements must be adequately substantiated
  - Belief in truth is not enough – there needs to be data at the time the materials are used
  - A single misstatement renders a product misbranded
- The totality of the circumstances must be considered when assessing IVD labeling for compliance

Labeling (cont'd)

- Labeling must contain "adequate directions for use" 21 U.S.C. § 352(f)(1)
- Off-label statements are often cited by FDA for violating this provision
- A violative statement in labeling does not become less violative because attributed to a third party, e.g., a testimonial or a letter
  - Never a defense that your competitor is engaging in the same conduct
- 21 C.F.R. contains detailed labeling requirements for IVDs

Misbranding

- In assessing whether misbranding occurred, FDA may consider whether material facts were omitted – 21 U.S.C. § 321(n)
  - Misbranding can be based on what a company does not say, as well as what it says
  - The omission can occur in oral or written materials
- The issue is whether the materials are false or misleading when taken as a whole

FDA Enforcement – Misbranding

- 21 C.F.R. § 801.6
  - This regulation states that "a false or misleading representation with respect to another device or drug or food or cosmetic" will render a device misbranded.
  - This is the only regulation relating specifically to device promotional activities
- Comparative claims more likely to be brought to FDA's attention through competitors

Advertising

- Not defined in the FDCA
- Would include radio, TV, and magazines
- Federal Trade Commission (FTC) has jurisdiction over device advertising other than for restricted devices
- FDA will use advertising to establish intended use of device
- Advertising must be carefully reviewed for compliance with law

Advertising and Promotion: the Internet

- FDA regulates material posted on the internet
- It is easy for FDA to, on its own initiative, identify violative company web site materials
- Many FDA warning letters have cited company web postings
- FDA will not develop an Internet-specific regulatory policy
- FDA may take action for off-label material that is directly linked to the company's web site

Advertising and Promotion: the Internet (cont'd)

- FDA has not taken action for a company's page if linked to the home page of an independent web site, e.g., NIH, which contains off-label information elsewhere on the site
  - Linking to the off-label page potentially would be problematic
- FDA has not objected to U.S. web sites containing a link to foreign promotional material, provided that it is clear in the U.S. site that the user is electing to go to non-U.S. site
  - The "two-click rule"
- FDA has sent some drug companies letters relating to their use of sponsored-links
- Social networking e.g., Facebook and Twitter, are creating issues and need to be used carefully

Social Media and FDA

- Social media tools present unique challenges in complying with legal and regulatory requirements
  - Adverse events: What are a company's responsibilities to track and report adverse events through media where it may be difficult to obtain sufficient information to report to FDA?
  - Transparency: Companies must ensure that they are transparent as to their involvement or sponsorship of social media communications
  - Control: Since social media/new media tools are beyond the company's control (e.g., sidewiki, Wikipedia), what responsibility attaches?
- To date, FDA has not provided any guidance

Off-Label Use

- Physicians have long been able to prescribe drugs for off-label uses
- The Food and Drug Administration Modernization Act of 1997 eliminated any doubt that physicians may prescribe devices for off-label uses
- Off-label uses of devices are recognized as being critical to the practice of modern medicine
- The issue for IVD companies is not the off-label use by the physician or laboratory, but the dissemination of off-label information by the company
  - But: Draft Research Use Only guidance does raise an issue over regulation based on use
- FDA has recognized that off-label use may be medically necessary

Off-Label Use (cont'd)

"While manufacturers may not themselves promote [off-label] uses, it is not unlawful for doctors to employ or prescribe medical products for 'unapproved' uses. Indeed, the FDA claims that it has 'long recognized the important role that some unapproved uses may play in the practice of medicine.'"

Washington Legal Foundation v Kessler, 880 F. Supp. 26, 28 n 1 (D.D.C. 1995) (citing FDA's memorandum supporting motion to dismiss).

- This does not give carte blanche to make off-label claims

Off-Label Use (cont'd)

- Labeled uses are determined by reference to the package insert or comparable document
  - Intended use
  - Indications for use
  - Population, e.g., pediatric or gerontology
  - Use with other products, e.g., instruments
- A company therefore can make off-label claims in a variety of ways

Promoting 510(k)-cleared device

- Companies submit a marketing application and obtain clearance for a specific intended use(s)
  - Other companies' marketing materials are irrelevant to determining your intended use
- Other intended uses outside of the cleared intended use are "off-label"
- Once 510(k) cleared, company can then freely advertise and promote product for that use
- Can promote only for cleared intended use
- Until 510(k) is cleared, cannot engage in these kinds of activities

Promoting 510(k)-cleared device (cont'd)

- Clearance of general intended use does not necessarily allow promotion of more specific intended use, e.g., a clearance for identifying a biomarker may not cover using the biomarker to diagnose a specific disease
  - FDA's "general vs. specific" policy is confusing
  - Lack of regulatory clarity regarding "general vs. specific" claims reinforces need to stay "on message"
- New intended use will require new 510(k)
- Making a more specific claim will generally require a new 510(k) clearance
- Intended use determined by the labeled intended use, not the data in the 510(k)

CME Programs

- FDA considers Continuing Medical Education programs sponsored by a device manufacturer to be evidence of the product's intended use but will not regulate the activity if it meets guidelines
- A speaker at a CME program can discuss off-label uses
- The key is the independence of the program
  - FDA's CME Guidance focuses on independence.
  - No company influence over content
  - Company does not determine invitation list
  - The CME provider is responsible for selecting speakers
  - There is opportunity to question the speakers
  - Programs meet established standards for CME programs
  - Disclosure of financial ties between the speaker and sponsor – undisclosed conflicts now present greater concerns

CME Programs (cont'd)

- It is essential that there be a contract with the CME provider establishing its independence
- A procedure should be in place to ensure that FDA guidelines are followed
- Programs conducted or organized by company employees are not CME programs
- Giving an unrestricted grant to a hospital does not qualify the program for CME status
- CME programs must be supported in conformance with company procedures
- A program is not within the CME "safe harbor" simply because it is educational and offered to physicians

FDA's Policy on Reprints

- Issued in January 2009
- Generally permits distribution of peer-reviewed reports for marketed devices, with caveats
  - Unabridged copy
  - No highlighting or marking-up
  - Accompanied by labeling
  - Not to be distributed with promotional materials
  - Affix a statement that the use has not been approved or cleared by FDA
  - Potential conflicts of interest by authors disclosed

FDA's Policy on Reprints (cont'd)

- Peer-reviewed does not always mean well-controlled
  - Are the data scientifically valid?
  - Was the study well-designed?
  - Have the results been replicated?
  - Are the results consistent with what is known about the product?
  - What kinds of caveats does the article contain?
  - Adequate number of subjects?

FDA's Policy on Reprints (cont'd)

- Not every published article should be distributed under FDA's policy
- Sales reps cannot use off-label reprints to promote products
- Distributing flawed articles could raise FDA, product liability and other legal issues

FDA Enforcement

- Untitled Letter
- Warning Letter – public
- Seizure – product
- Civil Penalties – corporate and individual
- Injunction – corporate and individual
- Prosecution – corporate and individual
- False Claims Act Implications
- Impact on corporate image

Conclusion

- FDA has broad jurisdiction over promotion of IVD products
- Companies need to understand requirements, review promotional materials, and train sales reps
- Failure to comply can result in FDA sanctions