Consistent with Labeling Final Guidance: Implications for Devices

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What is Labeling?

- “Labeling” is a key term in regulating promotional materials
- Labeling consists of “all labels and other written, printed, or graphic matter” on or “accompanying” a device -- 21 U.S.C. § 321(m)
- The material does not physically need to accompany the device to be labeling. Kordel v. US, 335 U.S. 345 (1948)

What is Advertising?

- Not defined in the Food, Drug, and Cosmetic Act (FDCA)
- Drug regulations state: “Advertisements subject to section 502(n) of the act include advertisements in published journals, magazines, other periodicals, and newspapers, and advertisements broadcast through media such as radio, television, and telephone communication systems.” 21 C.F.R. § 202.1(l)(1).

Basic Rule #1

- All labeling and advertising must promote devices only for a 510(k) cleared or PMA approved intended use
  - Creating a new intended use misbrands or adulterates the device in the absence of a new clearance or approval (FDCA secs. 502(o), 501(f)) and adequate instructions for use (FDCA sec. 502(f))

Basic Rule #2

- All promotional claims in labeling must have adequate data substantiation
  - A device is misbranded if its labeling is false or misleading in any particular (FDCA sec. 502(a))
  - Inadequate data makes claim false or misleading

Off-Label Promotion: Three Safe Harbors

- Unsolicited requests
- Good Reprint Practices
- Continuing Medical Education (CME) guidance

Unsolicited Requests

- Draft Guidance, "Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices" (Dec 2011)
  - Paradigm is scientist/medical officer providing balanced information to health care professional who inquires
  - May disseminate off-label information in manner prescribed in this guidance without being deemed to have promoted off-label

Good Reprint Practices Guidance

- Guidance for Industry, "Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices" (2009)

- Establishes parameters for disseminating journal articles and textbooks with off-label information

Continuing Medical Education (CME)

- FDA considers CME programs sponsored by a device manufacturer to be labeling
- Guidance, "Industry-Supported Scientific and Educational Activities" (2009).
- 12 factors to assess whether program is independent
  - *E.g.*, control of content and selection of moderators

Communications Consistent with FDA-Required Labeling (CFL)

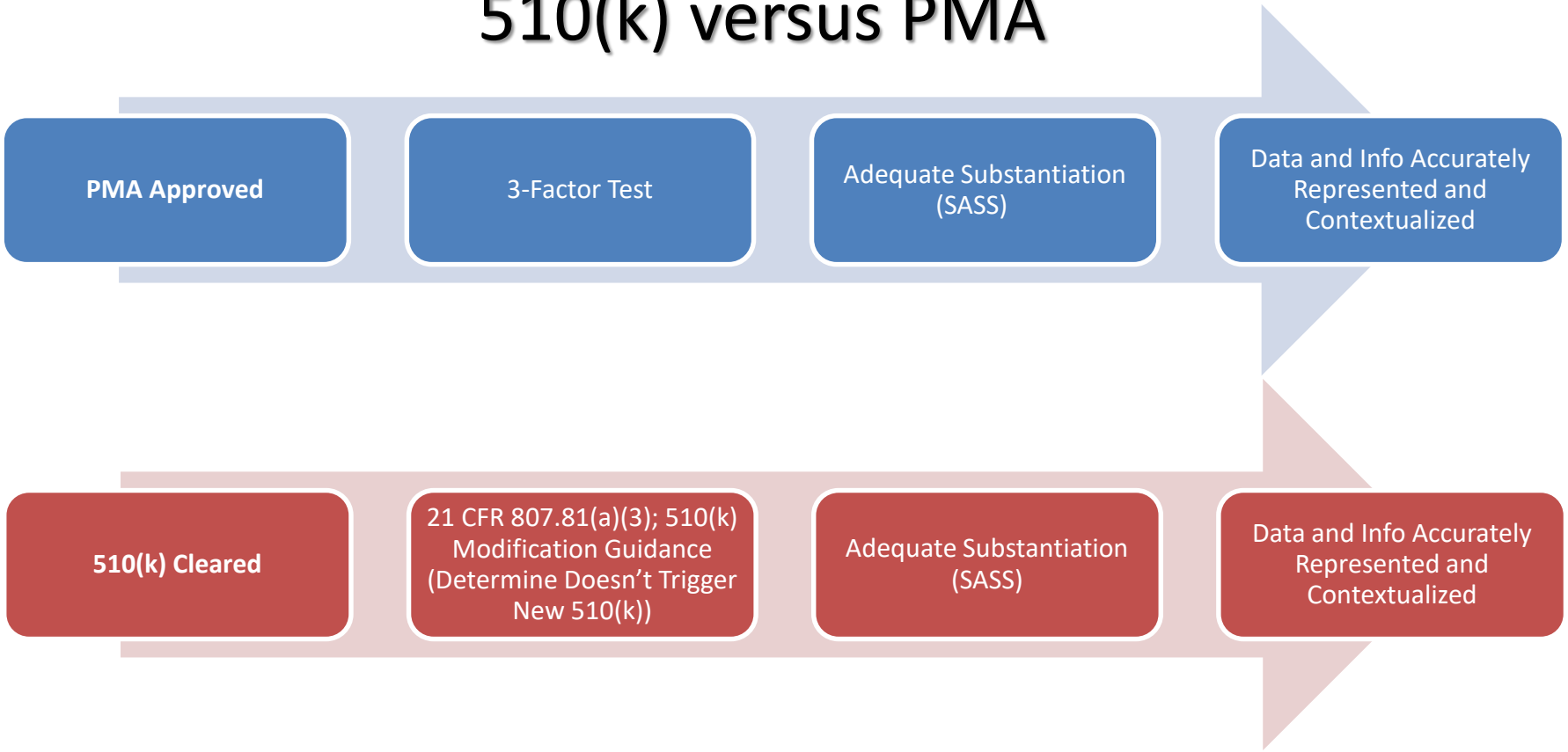
The Latest “Safe Harbor” Guidance – For “out of label” communications: Medical Product Communications That Are Consistent With the FDA-Required Labeling — Questions and Answers (2018)

- FDA’s position is that the FDA-required labeling is primary tool for necessary information for safe and effective use
- Guidance allows that information not in the labeling can be provided

3-Factor Test in Guidance Does Not Apply to 510(k)-Cleared or 510(k)-Exempt Devices!

- For 510(k)-cleared devices analyze communications (whether in labeling or otherwise) in accordance with 21 CFR 807.81(a)(3) and FDA's Guidance, "*Deciding When to Submit a 510(k) for a Change to an Existing Device*" (October 2016)
- For 510(k)-exempt devices, analyze communications in accordance with the limitations of exemptions at 21 CFR 862.9 to 892.9 and, for certain devices, in their classification regulation

Review Process for CFL Communication: 510(k) versus PMA



Three Key Factors to Determine If Communication Is Consistent with Labeling

- **Factor 1:** How the information in the product communication compares to the information about those conditions of use in the FDA-required labeling
  - Indication
  - Patient Population
  - Limitations and Directions for Use
  - Use Regimen
- **Factor 2**: Whether the representations/suggestions about use of the product in the product communication increase the potential for harm to health relative to the information reflected in the FDA-required labeling
- **Factor 3**: Whether the directions for use in the FDA-required labeling enable the product to be safely and effectively used under the conditions represented/suggested in the product communication

Implantable Device Example

- PMA approved implantable device
- Postmarket registry provides data suggesting reduced side effects with more shorter, frequent use
- Could be presented in promotion with appropriate caveats about post hoc, descriptive statistics

Adequate Substantiation Still Applies

- “To be truthful and nonmisleading, representations or suggestions made by firms about their products need to be grounded in fact and science and presented with appropriate context. Any data, studies, or analyses relied on should be scientifically appropriate and statistically sound to support the representations or suggestions made in a CFL promotional communication.”

CFL Review Process

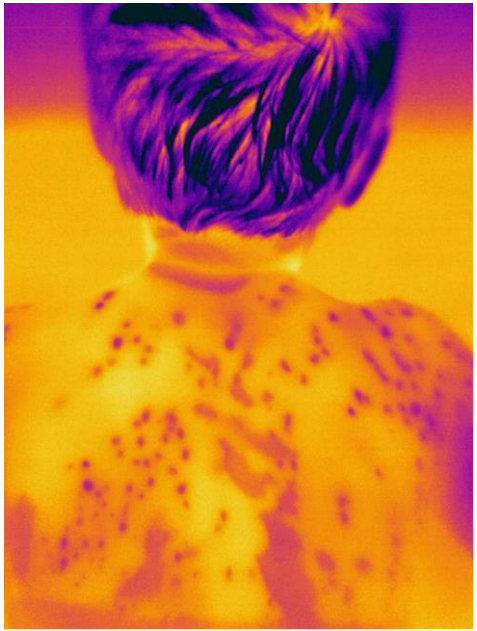
- **Caution:** Even if communication meets CFL Test, still consider specific communication in context of entire promotional campaign
- **Why?** CFL Communication will not alone be considered evidence of violation of FDCA. However, FDA may still consider CFL communication when assessing firm's conduct if there is other evidence of new intended use

If Not Consistent, Then What?

- “A determination that a product communication is not consistent with that product’s FDA-required labeling does not necessarily mean the communication is one that FDA would rely on as relevant to establishing a violation of FDA-administered legal authorities. There are other potentially relevant regulations, guidance documents, and policies that describe the Agency’s views and enforcement priorities that could apply in this situation.”

Case Study #1:
"Disease Awareness" for 510(k)-Cleared Device Device

- ABC Imaging, Inc. markets a diagnostic imaging device cleared under a 510(k) for the following indications:
  - Imaging system intended for viewing and digitally storing thermal images and patterns generated by the human body in the clinical, hospital and outpatient settings
  - For use in adult and pediatric populations



Case Study #1:
"Disease Awareness" for 510(k)-Cleared Device, Cont'd.

- ABC submitted a proposed IFU to CDRH's Office of Device Evaluation (ODE) during the 510(k) review
- The proposed labeling contained claims regarding use of the device for:
  - "breast screening,"
  - "early detection of abnormal changes"
  - "use as a adjunctive procedure"
  - "greater sensitivity and specificity" then other imaging devices
- ODE rejected these claims because ABC did not have adequate data to support the proposed claims
- In response to ODE's feedback, ABC revised its proposed labeling to remove these claims from the final IFU

Case Study #1:
"Disease Awareness" for 510(k)-Cleared Device, Cont'd.

- Four years later, ABC is aware that 40% of the HCPs who use its imaging device are using it as a breast cancer screening tool
- The business team would like to develop a "Breast Cancer Awareness" campaign to discuss the benefits of early screening
- They believe the CFL Guidance may provide a pathway for them to do this

➢ **You're ABC's Lawyer. How do you advise ABC?**

Case Study #2: "Comparative Safety" for PMA Device

- New Face, Inc. markets a single-use syringe dermal filler for aesthetic use
- The product is approved under a PMA for the following indication:
  - Correction of moderate to severe facial wrinkles and folds in patients 21 or over
- The IFU contains several warnings, including warnings related to the following issues:
  - Do not use if patient skin is inflamed or infected
  - Injection site reactions have been observed shortly after treatment
  - Do not introduce into the vasculature
  - Use care while injecting to avoid intravascular injections

Case Study #2: "Comparative Safety" for PMA Device, Cont'd.

- Analysis of MAUDE data and other post-market information shows an increase in adverse events related to intravascular injections for the dermal filler product category
- CDRH encourages dermal filler manufacturers to update their HCP labeling to provide heightened warnings/precautions regarding the potential risks and complications of intravascular injection
- New Face updates its HCP labeling to provide the proposed warnings and precautions suggested by FDA
- New Face also launches an HCP education/training program, including an interactive mobile application with video demos, educational information and HCP forums

Case Study #2: "Comparative Safety" for PMA Device, Cont'd.

- New Face, Inc. believes that the design features of its syringe and its enhanced HCP education/training program reduce the risk of intravascular injection compared to other fillers
- The business team would like to develop a "vascular safety" campaign to tout the superior safety profile of its syringe and HCP training protocol in reducing incidents of intravascular injection
- They believe the CFL Guidance may provide a pathway for them to do this.

➢ **You're New Face, Inc.'s Lawyer. How do you advise New Face, Inc.?**

Key Take-Aways

▪ Doesn't provide additional latitude on off-label	▪ Case-by-case analysis
▪ Doesn't move needle far on "out-of-label" communications for devices, but may impact certain claims (*e.g.*, long term data claims)	▪ For 510(k) devices, CFL analysis should be done through 510(k) modifications guidance
▪ Important to contextualize info and not overstate findings/conclusions and provide appropriate disclosures	▪ Consider documenting decision-making process for determining if claims fit the "consistent-with" framework