Commercialization of IVDs Labeled For Research Use Only or For Investigational Use Only

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In vitro Diagnostic Products

- 21CFR 809.3(a)
  - In vitro diagnostic products are those **reagents, instruments, and systems** intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the **collection, preparation, and examination of specimens** taken from the human body. [more]

FDA Oversight of IVDs: General controls

- Premarket review of class II, III, some class I devices
- Compliance with Quality System reg (GMP)
- Adverse event reports
- Recalls
- Other

Investigational Use Products

- Investigational phase:
  - Generally products whose design phase is complete
  - Investigations intended to generate data and information to support premarket application
  - Controlled use consistent with 21CFR 812
  - Investigational labeling required when shipping
  - Not a way to market products intended for clinical use outside of an investigation

Research Use Products

- Research phase
  - Generally in design phase, prior to implementation of design controls, to determine operating characteristics, etc
  - Also can be for products used in legitimate research to develop fundamental scientific knowledge
  - Regulatory requirement for labeling when shipped
    - Not subject to QS regs, other controls
  - Not a way to market products intended for ANY clinical use
    - "For **research** use only. Not for use in diagnostic procedures"

What's the Problem Here?

- Products marketed for clinical use but labeled RUO or IUO
  - Products lack FDA review, are generally not manufactured under GMP, lack all other general controls
- Manufacturers routinely shipping mislabeled products
  - Intentional
  - Unintentional
- Inappropriately labeled products include high risk products
  - Results not reliable; no performance assurance
  - Safety and effectiveness unknown
  - Putting patients at risk

Compliance Issues

- 21 CFR 801.4
  - In part "… [I]f a manufacturer knows, or has knowledge of facts that would give him notice that a device introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a device which accords with such other uses to which the article is to be put"
  - Interpret: If a manufacturer is marketing a product for clinical use, he is required to label it for clinical use ("For in vitro diagnostic use"). Logically, to use this label, the product must comply with FDA regs.

Compliance Actions

- Misbranded and adulterated devices are subject to FDA compliance actions
  - Misbranding (FFDCA Sec 502)
    - False and misleading labeling
    - Failure to register
    - Failure to provide directions for use and warnings
  - Adulteration (FFDCA Sec 501)
    - Failure to obtain premarket approval

Not a New Problem

- 1973 FR notice. “In vitro diagnostic products for human use. Labeling requirements and procedures for development”
  - Establishes labeling for research-use and investigational products for shipping of products “prior to commercial marketing”
- 1997 ASR rule intended to curb use of unregulated products in LDTs
  - See 61 FR 10484 regarding concerns that LDTs were using reagents of undefined and uncertain quality

Not a New Problem

- Draft Compliance Policy Guide issued (1997) but never finalized
  - Addressed appropriate uses of RUO/IUO labeling
- Warning letters and untitled letters issued for devices mislabeled as RUO/IUO
  - Address 501 and 502 issues

RUO/IUO Compliance

- Problems exacerbated recently
  - Final ASR Guidance, September 7, 2007
  - Mfrs change labels from ASR to RUO or IUO to avoid premarket submission for IVD kits
  - Purposeful marketing for clinical use
  - Affecting many molecular Dx

RUO/IUO Compliance

- Ongoing problem with reagents, instruments previously only used for basic research
  - Translation of research into clinical use
  - Little corresponding translation of devices to IVD status
  - Cannot clear/approve devices using reagents/instruments lacking essential controls

Examples of Problems

- RUO-labeled products with:
  - "intended uses"
  - Clinical interpretation information
  - Performance characteristics
  - Statements about diagnostic use
- IUO-labeled products with:
  - Long-term clinical use without IRB, IC

Mind Your R' and I's

- FDA may take compliance actions against manufacturers for clearly adulterated/misbranded products
- Intent may indicated by labeling claims, advertising, oral or written statements
- Sponsor responsibility for addressing uses and providing appropriate labeling

Guidance

- FDA working on guidance
  - Similar to CPG
  - Explains legal, regulatory requirements
  - Nothing new
  - No availability date yet

NEW ISSUE
Importation of RUO products

- RUO products generally exempt from most regulatory requirements
- BUT, *imported* RUO products are not specifically exempt from establishment registration and device listing provisions codified at 21 CFR 807.65.
- FDA exercising enforcement discretion
  - Does not intend to enforce establishment registration and device listing requirements for imported RUO products.
  - To facilitate entry of RUO IVD products into the United States, an appropriate product code should be identified on required importation documents.
  - See product code database for 6 RUO product codes
  - For biologics, contact CBER for information

PreIDEs

- What is a preIDE?
  - Generally, not specifically related to an IDE
  - A way for industry to check its plans prior to starting studies
    - Not a request to FDA to design studies for industry
  - Non-binding, but deviations from FDA advice will likely be questioned
    - Alternative, scientifically justified approach OK
    - Simply ignore FDA advice at your peril
  - Currently free of charge

Tips for preIDEs

You may want to use a preIDE if:

- You/your company is new to regulation
- Your device has a new intended use
- Your device uses new technology
- Your device will need a clinical study (and thus a design)
- You have any concerns about what you are planning

What we do

- Provide commentary on your stated plans
- Suggest alternative studies, etc
- Sometimes provide a provisional classification determination based in stated intended use
- Sometimes, point out that not enough information is available to commemt

What we don't do

- Design studies for you
- Answer questions you didn't ask
- Provide an final classification determination
- "Pre-review" your regulatory submission
- Act as your regulatory consultant

How do I initiate a preIDE?

- PreIDEs are handled by the review division that would review the final submission
  - DMD (Sally Hojvat, Uwe Scherf)
  - DIHD (Maria Chan, Reena Philip)
  - DCTD (Courtney Harper, Carol Benson)
- Contact DivDir or Deputy DivDir for info

PreIDE Process

- Usually preIDE submission is assigned to one reviewer or a team
- Review may include request for additional information
- Reviewer/team provides feedback in form of letter: 60 TAT for review
- Company may seek F2F meeting if needed

Questions?

- Thanks!
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