FDA Regulation of RUO/IUO IVD Products

FDA-Industry IVD Roundtable

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http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm253307.htm

Draft Guidance for Industry and FDA Staff - Commercially Distributed In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Frequently Asked Questions

DRAFT GUIDANCE

PDF Printer Version

This guidance document is being distributed for comment purposes only.

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You should submit comments and suggestions regarding this draft document within **90** days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document contact Tonya Wilbon at 301-796-6224 (tonya.wilbon@fda.hhs.gov). For questions regarding this document as applied to devices regulated by CBER contact the Office of Communication, Outreach and Development (OCOD), 1-800-835-4709 or 301-827-1800, or email ocod @fda.hhs.gov.

Center for Devices and Radiological Health
CDRH

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of In Vitro Diagnostic Device Evaluation and Safety

Center for Biologic Evaluation and Research

Research Use Only (RUO) Products

- Defined in 21 CFR Part 809(c)(2)(i)

- Laboratory Research Phase of Development
  - Generally prior to implementation of design controls to evaluate operating characteristics
  - Examples:
    - research to identify IVD kit methodology, components, analytes in development etc.
    - Research on instrumentation under development to determine correct settings, basic operational characteristics etc.

- Intended for research to develop fundamental scientific knowledge related to human disease/conditions
  - Example: Reagent intended to be used to isolate a gene linked with a particular disease/condition and are not intended to produce results for clinical use

RUO Products – Regulatory Requirements

- Premarket Review Requirements: Not Applicable
- QSR Requirements: Not Applicable
- Registration and Listing outlined in 21 CFR 807.40
  - FDA is utilizing enforcement discretion authority to not require foreign manufacturers and exporter of certain RUO products to register and list
- Labeling Requirements listed in 21 CFR 809.10(c)(2)(i)
  - Must prominently display statement:
    "For Research Use Only. Not for use in diagnostic procedures"
  - Not a way to market products intended for ANY clinical use

Investigational Use Products

- Investigational phase:

  Disclaimer: For the purpose of this presentation – will not discuss investigational-phase products subject to IDE requirements (21 CFR 812)

  - Defined in 21 CFR 809.10(c)(2)(ii)
  - Generally products whose design phase is complete
  - Investigations tend to generate data and information to support premarket application
    - Example: Diagnostic Test Kit used on banked specimens derived from humans to perform analytical validation of the kit
  - Not a way to market products intended for clinical use outside of an investigation

Investigational Use Products – Regulatory Requirements

For IUO products not subject to IDE Regulations (21 CFR 812):

- Premarket Requirements: Not Applicable
- QSR Requirements: Not applicable
- Labeling Requirements listed in 21 CFR 809.10(c)(2)(i)
  - Must prominently display statement:

    "For Investigational Use Only. The performance characteristics of this product have not been established"

What's the Problem Here?

- Products marketed/shipped intentionally/unintentionally for clinical use but labeled RUO/IUO
- Inappropriately labeled products include high risk products
- Products lack
  - FDA review
  - Generally not manufactured under GMP
  - All other general controls of other medical devices

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")
    - Product therefore must comply with FDA regulations

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 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 labeling
- Warning letters and untitled letters issued for devices mislabeled as RUO/IUO
  - Address 501 and 502 issues

RUO Compliance

- Problems exacerbated recently
  - Final ASR Guidance, September 7, 2007
  - Manufacturers change labels from ASR to RUO or IUO to avoid premarket submission for IVD kits
  - Purposeful marketing for clinical use
- New guidance document
  - Aimed at **manufacturers** to clarify how RUO/IUO devices may be labeled and marketed

Acceptable Marketing Practices for RUO/IUO Practices

- RUO
  - May market for research use by general discovery laboratories
- IUO
  - May market/promote use in clinical investigations exempt from 21 CFR 812

Unacceptable RUO/IUO Marketing Practices

- RUO-labeled products with:
  - Naming the product in such a way so as to insinuate clinical diagnostic use
  - “intended uses”
  - Clinical interpretation information
  - Performance characteristics
  - Statements about diagnostic use
  - Statements promoting validation of component for clinical diagnostic use
- IUO-labeled products with:
  - Promotion of IUO product for non-investigational clinical use
  - Promotion of IUO product for use in an investigation subject to 21 CFR 812

Unacceptable RUO/IUO Marketing Practices

- Sales to clinical laboratories:
  - If the manufacturer **clearly** markets RUO/IUO product to laboratories for clinical use, but fails to meet applicable requirements
  - Manufacturer provides support for activities related to clinical use of the test
    - Technical support
    - Assistance in clinical diagnostic test validation, etc.

Clearance/Approval of IUO/RUO Reagents/Instruments

- IUO/RUO Reagents/Instruments may obtain FDA clearance/approval
  - IVD manufacturer must submit information on the IUO/RUO component as part of a premarket submission
  - Upon clearance/approval of the premarket submission, RUO/IUO product may be relabeled only for use with that specific IVD product
    - If not manufactured by the submission sponsor
      - Relabel reagent product and include as a component of the kit
      - May be a problem if RUO/IUO product is an instrument

Research Use Only Products – Regulatory Requirements con't.

- **RUO Product Codes**
  - Six product codes have been established that must be used when declaring import entry of certain RUO products:
    - **Hematology RUO IVD Products** **OTQ**
    - **Clinical Chemistry RUO IVD Products** **OTV**
    - **Clinical Toxicology RUO IVD Products** **OTW**
    - **Pathology RUO IVD Products** **OTU**
    - **Microbiology RUO IVD Products** **OTT**
    - **Immunology RUO IVD Products** **OTR**

Thank you

Questions?