



FDA Regulation of RUO/IUO IVD Products

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Katie Serrano



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Draft Guidance for Industry and FDA Staff - Commercially Distributed In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Frequently Asked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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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document within **90** days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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.



**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 not intended to produce results for clinical use

Research Use Products – Regulatory Requirements

- Premarket Review Requirements: Not Applicable
- QS reg Requirements: Not Applicable
- Registration and Listing outlined in 21 CFR 807.40
 - FDA is utilizing enforcement discretion authority to not require foreign manufacturers and exporters 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

Research Use Only Products – Regulatory Requirements Cnt.

- **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

Investigational Use Products

- Investigational phase:

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

- Defined in 21 CFR 809(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
- QS reg 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, are generally not manufactured under GMP, lack all other general controls of other medical devices

Compliance Issues

- 21 CFR 801.4
 - In part “The words intended uses. . . refer to the objective intent. . . The objective intent . . . is determined by [the manufacturer’s] expressions or may be shown by the circumstances surrounding the distribution of the article. . . It may be shown by the circumstances that the article is, with the knowledge of [the manufacturer] offered and used for a purpose for which it is neither labeled nor advertised. . . ”
- 21 USCS 321 (bb)
 - The terms “Knowingly” or “Knew” means that a person, with respect to information:
 - Has actual knowledge of the information, or
 - Acts in deliberate ignorance or reckless disregard of the truth or falsity of the information

Interpretation

- If the circumstances surrounding the use of an RUO product overwhelmingly suggest to the manufacturer that the product is used clinically:
 - The manufacturer should label the product accordingly (“For In Vitro Diagnostic Use”)
 - Product should comply with applicable 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

- 1972 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

Marketing Practices Consistent with RUO/IUO Labeling

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

Marketing Practices Inconsistent with RUO/IUO Labeling

- RUO-labeled products with:
 - Product names that 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

Marketing Practices Inconsistent with RUO/IUO Labeling

- Sales to clinical laboratories when the manufacturer **knows or has reason to know** of clinical diagnostic use of the product
 - FDA particularly concerned with manufacturers whose greatest market share comes from clinical diagnostic use
 - Note: FDA does not ask for manufacturers to “police customers”, however:
 - Manufacturers generally understand their customer base
 - Sales information may be one piece of evidence considered when determining “objective intent” of the product
- Provision of Certain Types of Technical Support
 - Assistance with clinical validation, etc.
 - Not generally referring to generic maintenance of instruments etc.

Clearance/Approval of IUO/RUO Reagents/Instruments

- IUO/RUO Reagents/Instruments may obtain FDA clearance/approval
 - Manufacturer of IVD must submit information on the IUO/RUO component as part of a premarket application
 - Upon clearance/approval of the premarket submission RUO/IUO product may be relabeled only for use with that specific IVD product



- Thanks!