RUO

FDA-Industry IVD Roundtable Meeting

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Outline

- Definitions and basic facts
  - IVD
  - RUO
  - IUO
- Issues overview
  - RUO instrumentation
  - RUO reagents
- Guidance
  - Ancillary reagents

Definitions

- IVD – for *in vitro* diagnostic use
  - "*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. … use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the act), and may also be biological products subject to section 351 of the Public Health Service Act." 21 CFR 809.3(a).

Definitions

- RUO – research use only - labeled under 809.10(c)(2)(i)
  - A product in the laboratory research phase of development, **not** represented as an effective in vitro diagnostic product, all labeling bears the statement, prominently placed: "For Research Use Only. Not for use in diagnostic procedures."
- IUO – investigational use only – labeled under 809.10(c)(2)(ii)
  - A product shipped or delivered for testing prior to full commercial marketing (for example, for use on specimens derived from humans to compare the usefulness of the product with other products or procedures which are in current use or recognized as useful), all labeling bears the statement, prominently placed: "For Investigational Use Only. The performance characteristics of this product have not been established."

RUO product uses

- To evaluate design, limit-scale performance, usability
- Test, instrumentation, reagents that are under development
- Certain products intended for basic life-science research, and not intended to be further developed for clinical use

What should not be labeled RUO?

- Products that would be considered misbranded if labeled RUO:
  - Products intended for clinical investigation
  - Products intended for clinical use:
    - Diagnosis
    - Prognosis
    - Monitoring
    - etc

IUO product types

- Products that are object of an investigation (21 CFR 812.3(g)
- May be subject to 21 CFR part 812 (IDE)
- Example: products evaluated in comparison studies that use archived specimens to determine product performance characteristics.

What should not be labeled IUO?

- Products intended for non-investigational purposes, such as clinical use outside the investigation

- IUO products that are subject to 21 CFR 812 (IDE) should be labeled per 21 CFR 812.5 [and not 809.10(c)(2)(ii)]

- IUO products exempt from 21 CFR 812 under 812.2(c)(3) should be labeled per 21 CFR 809.10(c)(2)(ii)

GMP compliance?

- RUO and IUO products are **not** required to be manufactured in compliance with QS regulation (21CFR part 820), except products under 812.1 IDE (21 CFR 820.30, design controls)

Why RUO issues?

- RUO use and labeling defined in regulations

- However, despite regulations:
  - RUO labeled products sometimes promoted or used instead – or as parts – of IVDs

Background

- Public and private enterprise leads to sequencing of human genome, large SNP databases
- Advances in technology allow high throughput, multiplexed, miniaturized measurements of human genetic variation
  - Gene expression
  - SNPs
  - Proteomics
  - Copy number

Translation - problems

- Use of research tools (e.g., PCR, arrays, sequencers, etc) to translate scientific findings into human health outcomes in basic science labs

- Industries and clinical labs (particularly molecular diagnostic labs) - transfer research tools into diagnostic space by incorporating RUO reagents and instruments into assays

Two Main IVD Models

- Traditional
  - Complete systems provided by one manufacturer
- Mix-and-match
  - Systems made up of multiple pieces mfr'd and marketed by different entities

➢ A fundamental problem:

  - Little (if any) comprehension of QS Reg requirements

RUO Problem

CDRH and CBER

- Recognized as arising issue with increasing number of Mol Dx submissions
- Clearance of devices with RUO elements would be problematic (i.e. labeled as not to be used in diagnostic procedures)
- Relabeling (to RUO) of previously mislabeled (e.g. ASR) products → some kits labeled RUO but marketed for clinical use

Why is it a problem?

- RUO reagents, platforms generally not manufactured under GMP or QS
  - Performance variable between lots, instruments
- The majority of reagents not interchangeable
  - Performance generally optimized to work with specific buffers and conditions
- IP issues
  - Licenses preclude from marketing for diagnostic use
  - Device mfr need business agreement with ancillary reagents mfr

Mislabeled IVDs

- Labeling a device intended for clinical use with RUO statements:
  - misbranding
  - adulteration
- RUO products should not be marketed for clinical use
- Appropriate RUO labeling:
  - no clinical statements
  - no diagnostic information
  - no statements about disease association

Addressing the problem

- Number of presentations and discussions with industry on unsuitability of RUO for Dx use
- FDA intercenter discussions and consults
- Development of some creative solutions (e.g. ancillary reagent model)
- Compliance actions for misbranded/adulterated RUO-labeled IVDs

Where are we now?

Recent RUO issues – general examples:

- RUO enzyme issues
- Companion Dx (RUO instrumentation issues)
- RUO sequencer issues

The usual suspects - instruments

- Real-time thermocyclers
- Automated nucleic acid extraction systems
- Sequencers / Genetic Analyzers
- Microarray scanners

➢ **Currently many IVD versions available or planned**

Regulatory considerations – classification for instrumentation

- 21 CFR 862.2570 - Instrumentation for clinical multiplex test systems
  - ABI 7500 Fast Dx (cleared 9/08) / Product Code: NSU
  - Cepheid GeneXpert (cleared 9/09) / Product Code: **OOI** (Real-time nucleic acid amplification system)

- Sequencers/Genetic Analyzers
  - 21 CFR 862.2570 - Instrumentation for clinical multiplex test systems
  - **Separate Product Code**

Ancillary reagents

- What are they?
  - Described in RVP SCGD (Class II Special Controls Guidance Document: Respiratory Viral Panel Multiplex Nucleic Acid Assay):
  - Ancillary reagents are those reagents that a manufacturer specifies in device labeling as "required but not provided" in order to carry out the assay as indicated in its instructions for use and to achieve the test performance claimed in labeling for the assay.

Ancillary reagents

- Why are they a problem?
  - "… ancillary reagents of concern are those that must be **specified** according to manufacturer and catalog or product number, or other specific designation, in order for your device to achieve its labeled performance characteristics. **For example, if your device labeling specifies the use of Brand X DNA amplification enzyme**, and use of **any other** DNA amplification enzyme **may alter the performance** characteristics of your device from that reported in your labeling, then Brand X DNA amplification enzyme is an ancillary reagent of concern for the purposes of this document."

The usual suspects – reagents

- **Individual reagents**
  - **Enzymes**
    - **DNA Taq Polymerases**
    - **Reverse Transcriptases**
    - **Nucleases**
    - **Restriction endonucleases**
- **Cell lines used for controls**
- **Accessory reagents/equipment (platform / instrument specific)**
  - **Consumables & reagents**
- **Kits for:**
  - **DNA amplification**
  - **Detection**
  - **Nucleic acid Extraction - *manual* extraction or *automated* extraction (with specific instrument requirements)**
  - **Labeling kits for nucleic acid for detection methods**

Does my device contain RUO products? How do I find out?

- **Your** responsibility to address your labeling
- RUO problems with parts of the assays are often an issue with molecular based devices
  - Check reagents/equipment that are required but not provided for your assay
  - Check web Registration and Listing Database

    Possible problems:
    - Reagents might be listed under wrong regulation or product code
    - Might be listed as "multiple products" – need to contact manufacturer

What else to check?

- Check manufacturer website
  - Item webpage
  - Package inserts, brochures, user manuals, installation and safety manuals (instruments)
  - Warranty or “terms and conditions”
  - License agreements
- Ask manufacturer for product labeling

RUO reagents – ancillary reagent issues

- **Section 5.C Ancillary reagents (cont. from RVP SCGD):**
  - Elements to address:
    - Risk assessment (including reagent variability/quality, instructions inconsistencies)
      - Describe risk mitigation (necessary controls), e.g.
        - » User labeling to assure appropriate use of ancillary reagents (see “Labeling” for further discussion of labeling).
        - » Plans for assessing user compliance with labeling instructions regarding ancillary reagents.
        - » Material specifications for ancillary reagents.
        - » Identification of reagent lots that will allow appropriate performance of your device.

RUO reagents – ancillary reagent issues

- **Section 8.d Directions for use**
  - For test systems that call for ancillary reagents of concern:
    - "Emphasize through conspicuous labeling that proper product performance requires use of specific ancillary reagents as directed
    - Assure that users can clearly identify which ancillary reagents are suitable for use with your test. (e.g. specific lots)
    - Assess any risks of using wrong instructions for use (if there is a conflict)

Are we there yet?

- Not yet, but getting there:
  - Instrument manufacturers considering or developing instruments to market for IVD use
  - GMP enzymes becoming available
- Device manufacturers considering 3rd party labeling or regulatory issues
- Some IVDs and LDTs cleared or approved with potential workarounds

Conclusions

- Products labeled RUO should not be used for clinical diagnostics
- Instrumentation used for clinical Dx should be manufactured under GMP/QS
- Ancillary reagents required for diagnostic tests need to be brought under device manufacturers' QS