Clinical Trials and Investigational Device Exemptions

FDA Small Business
Regulatory Education for Industry (REdI)
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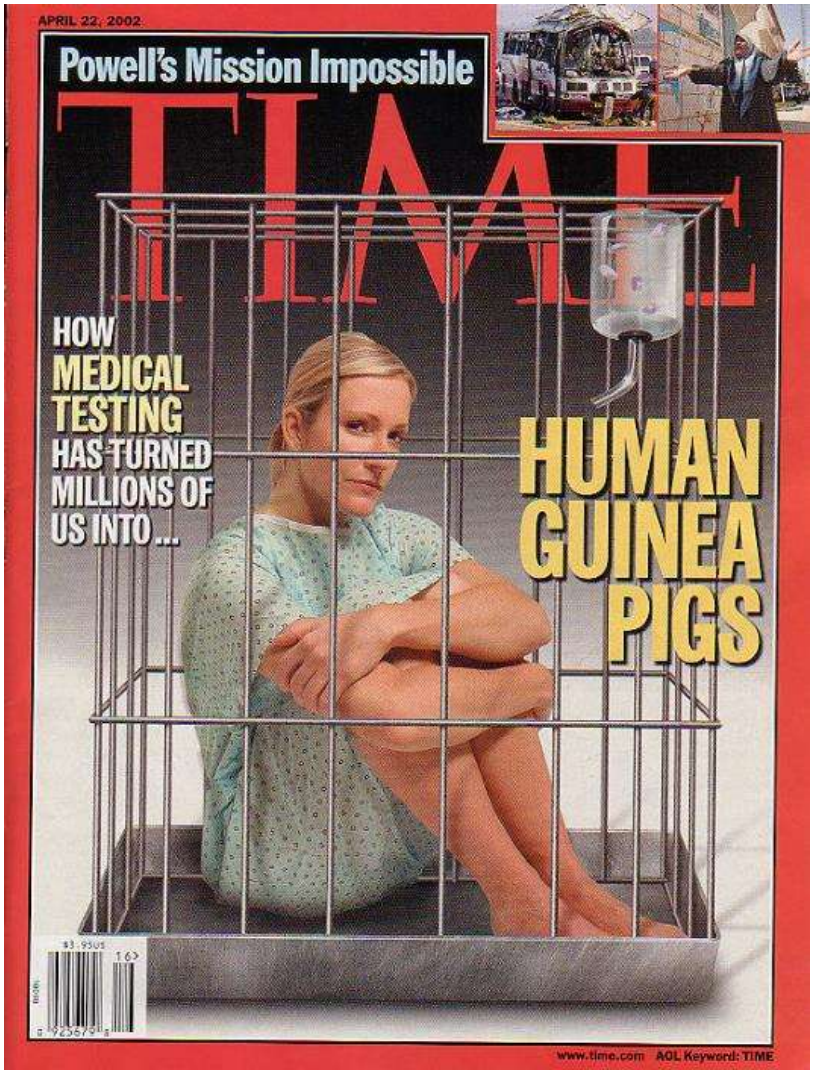
Innovation *and Protection*



Learning Objectives

- To understand the regulatory context of device clinical investigations
- To understand the requirements around off-label use
- To understand expanded access provisions

What is an IDE?

When is one needed?

Investigational Device Exemption

- Established in 21 CFR Part 812
- An IDE is a **regulatory submission** that permits clinical investigation of devices.
- FDA approval of an IDE is required for study of:
  - a **significant risk device** which is **not approved for the indication being studied**.

Common IDE Studies

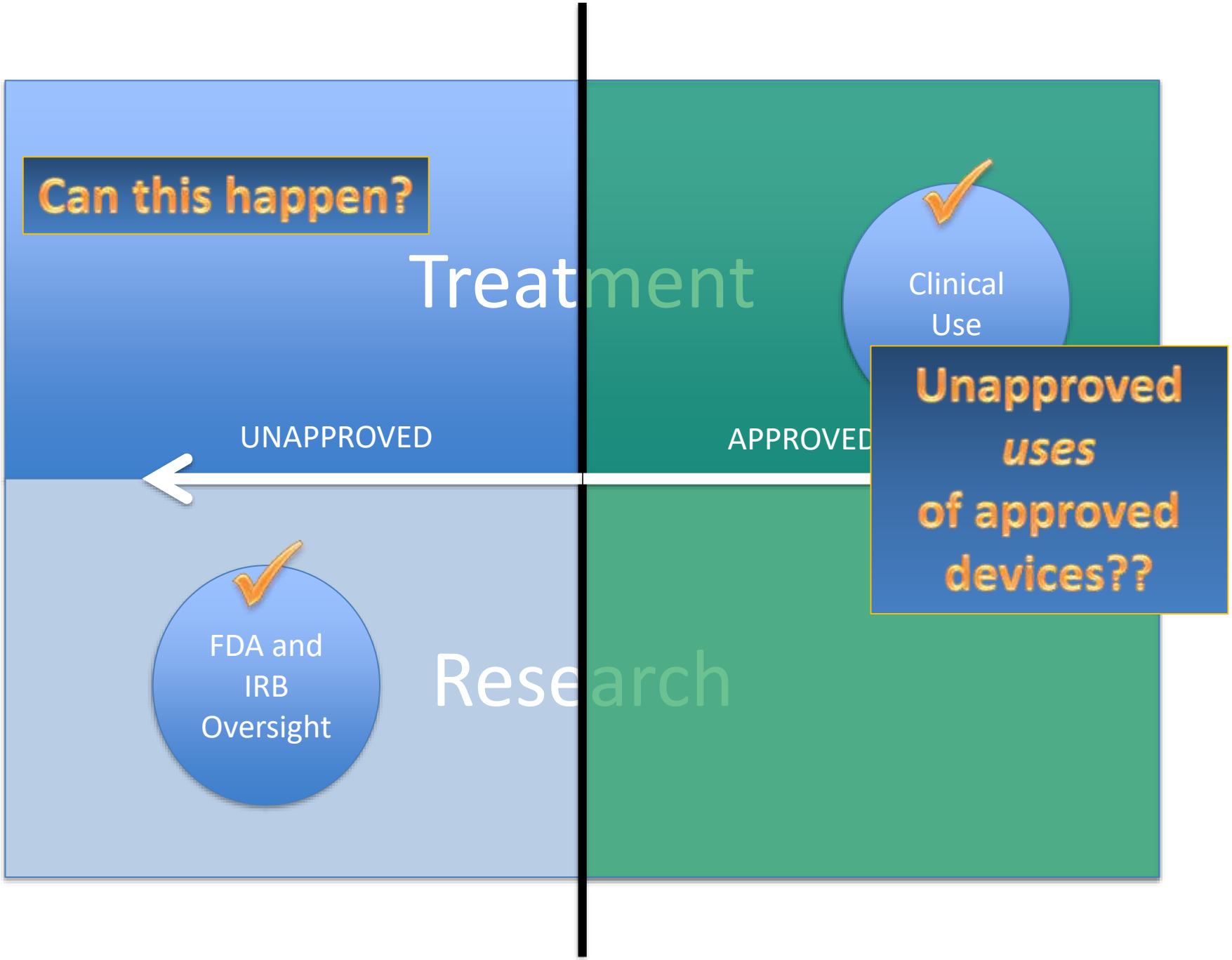
- To **support marketing** application [PMA, HDE, 510(k) or De Novo]
  - New device
  - New use of legally marketed device
- To gain **initial safety and effectiveness** information to support further study
- Sponsor-investigator studies of unapproved devices or new intended use of approved device (even if **no marketing** application planned)

FDA Decisions on IDE Application

- Made within **30 days**
- Decisions:
  - Approval
  - Approval with conditions
  - Disapproval
- **Disapproval** is appropriate when:
  - Probable risks to patients are not outweighed by anticipated benefits and importance of knowledge to be gained
  - Study doesn't pose a reasonable scientific question and/or is not designed to collect data related to that scientific question

Key Provisions of the IDE Regulation

- Describes **applicability** of the IDE regulations
- Outlines the contents of the **IDE application**
- Describes **FDA actions** on IDE applications
- Describes **human subject protection** requirements
  - informed consent and IRB review
- Assigns **responsibilities** to all participants in clinical investigation – Monitoring, Records, Reporting


Can this happen?
Treatment
Clinical Use
Unapproved uses of approved devices??
UNAPPROVED
APPROVED
FDA and IRB Oversight
Research

Off-Label Use

What is Off-Label Use?

- Use of a **legally marketed device**
- In a manner inconsistent with product labeling
- Generally for a different indication

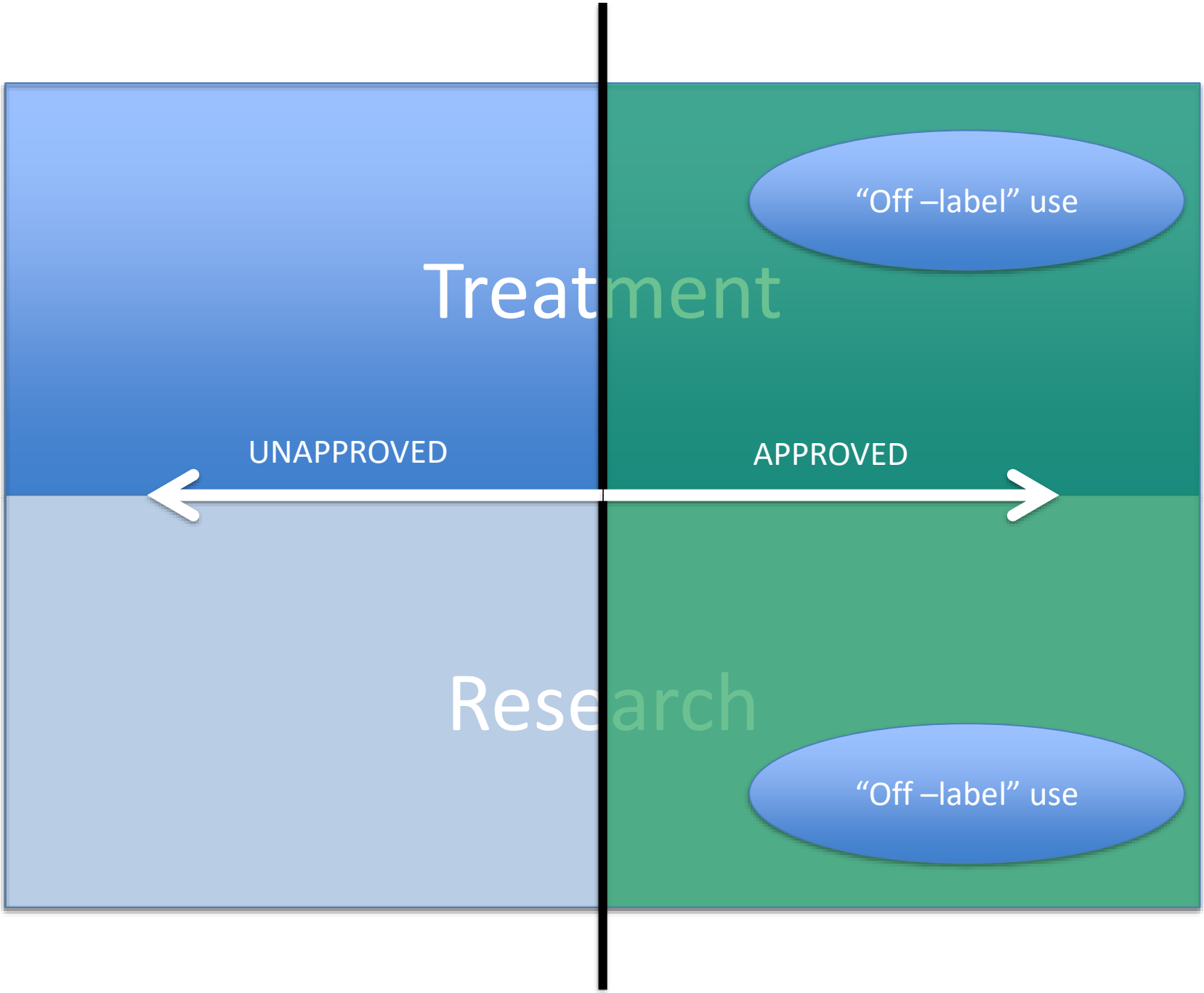
What is Labeling?

- **Defined** in 21 CFR 801
- **Explains**:
  - legally-marketed conditions of use (indications)
  - how to safely and effectively use the device
- **Includes**:
  - Packaging, User/Technical Manual
  - Indications for Use, Instructions for Use

Important to FDA device clearance/approval process

Striking Balance

- FDA doesn’t interfere with good medical practice in best interest of patients
- Off-label use may lead to approvals for new or expanded indications
- Laws, regulations, and CDRH programs aim to leverage information about off-label use while protecting patients


Treatment
"Off –label" use
UNAPPROVED
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Off-Label Use: Treatment

"Practice of Medicine"

Nothing in this Act shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any ***legally marketed device*** *to a patient for any condition or disease within a legitimate health care practitioner-patient relationship….*

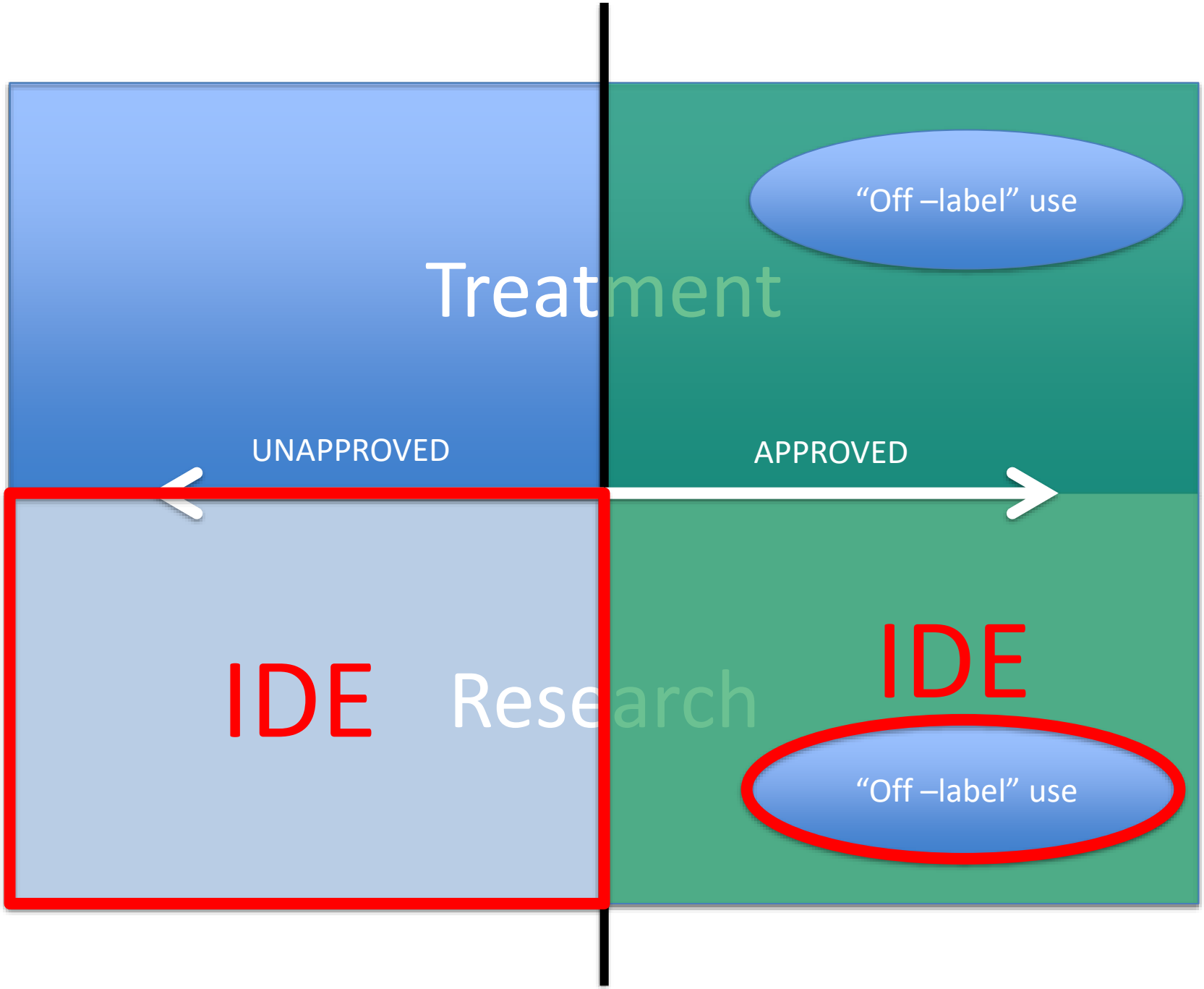
From Section 1006 of the FD&C Act

Practice of Medicine

- Physicians **can** use approved devices in off-label manner to **treat** a patient within their best judgment

- **Physician Responsibilities:**
  - be well informed about the product,
  - base device use on firm scientific rationale and on sound medical evidence, and
  - maintain records of the product's use and effects.
    - Note: Institutional IRB policies may exist

- Prior approval from FDA not required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Off-label Use: Research

- Investigations **to determine safety and effectiveness of off-label use** fall under IDE regulation
  - If significant risk, requires submission of an IDE application to FDA, if significant risk
  - Subject to informed consent and IRB requirements

Research: On- vs. Off-Label

- **On-label**: A device "…that is used or investigated in accordance with the indications in the labeling…" is **exempt** from the IDE regulations (812.2(c)(2))
- Whether a study is on- or off-label may not be clear, for example
  - General to Specific
  - Study of group in "Warnings" section of labeling

General-to-Specific Example

- Surgical ablation devices may be cleared with a general indication of “ablation of cardiac tissue”
- **Question:** Is a study of the use of these devices for treating atrial fibrillation (AF) considered on-label or off-label?
- **Answer:** **Off-label.**

  Treatment of AF would be considered a new intended use. The clinical endpoints for the general use can not be applied to the specific use (ablating tissue vs. health outcomes such as freedom from AF)

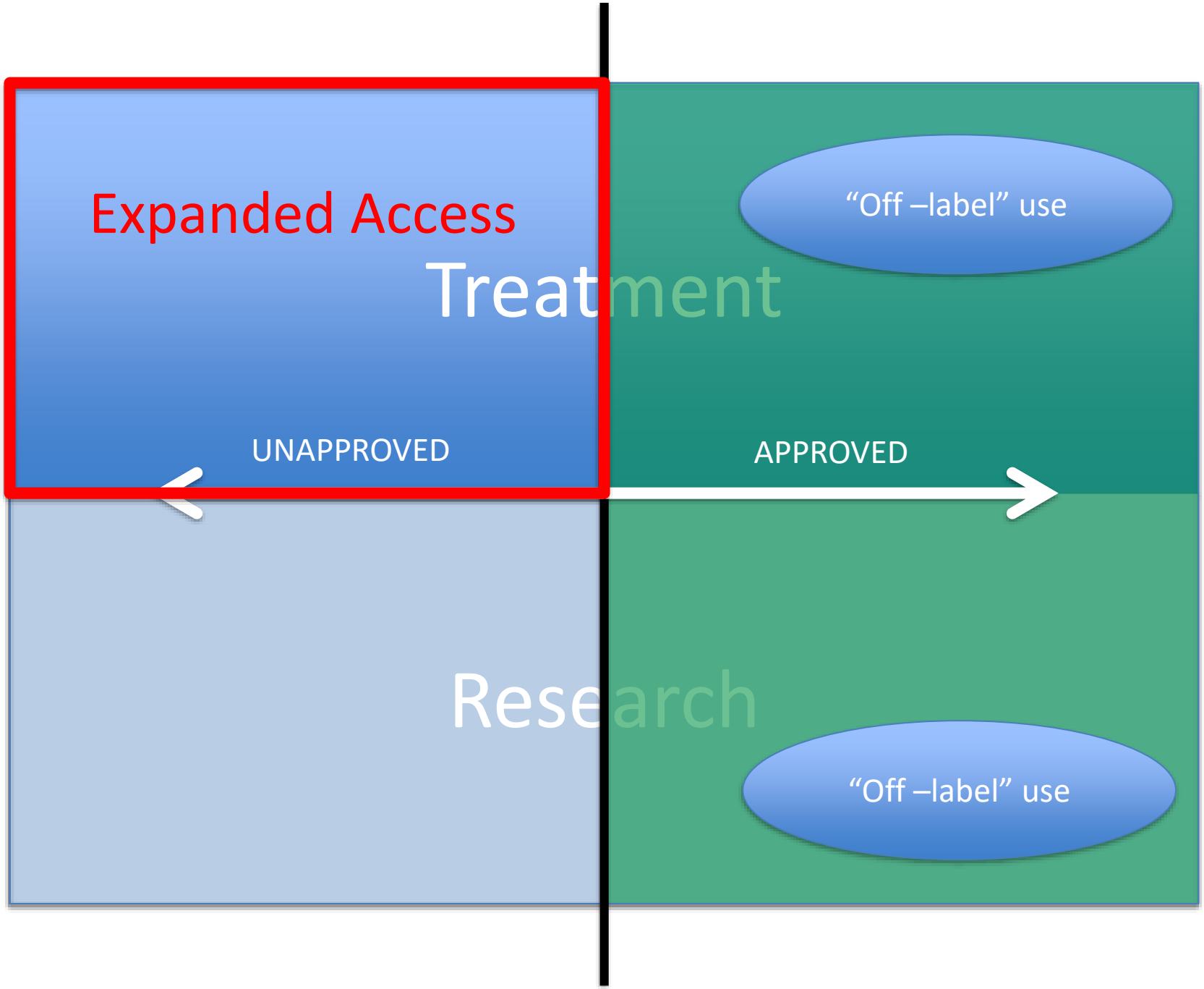
Off-Label Use vs. Research

- Clinical Trials Program receives many inquiries about what is research/investigation:
  - Device registries?
  - Surveillance?
  - "Retrospective" studies of off-label use?
- It **might** be an FDA-regulated investigation if:
  - There is a protocol
  - There are case report forms
  - Existence of the data collection effort impacts treatment decisions

Real-World Evidence

- **FDA Guidance**: *Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices*
- FDA actively working to develop policy outlining regulatory requirements for generation of real-world evidence
- Contact FDA for questions about whether a research activity is considered a FDA-regulated investigation

Expanded Access


Expanded Access
Treatment
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What is Expanded Access?

- Use of an investigational device outside of a clinical study:
  - to save the life of a patient or to help a patient suffering from a serious disease or condition; and
  - for which no other alternative therapy exists.

- Three types
  - Emergency Use
  - Compassionate Use
  - Treatment Use

Resource:
Expanded Access for Medical Devices

Striking Balance

- All expanded access has patient protections in place to balance uncertainties of unapproved products

- We want to balance individual patient access with the need for evidence generation to support broader approval

What is Emergency Use?

- The shipment of investigational drugs or investigational devices,
- For the diagnosis, monitoring, or treatment of a serious disease or condition,
- In emergency situations.

Emergency Use

- **Criteria**
  - Life-threatening or serious disease or condition
    - includes sight-threatening and limb-threatening conditions as well as other situations involving risk of irreversible morbidity.
  - No alternative therapy exists
  - No time to obtain FDA approval
- Must be **reported** to FDA and IRB within 5 days of use

Emergency Use: Report Contents

- Device description
- Description of patient's condition and circumstances necessitating treatment
- Discussion of why alternative therapies were unsatisfactory
- Clarity on urgency of use
- **Patient protection measures** followed
- Outcome of procedure and any adverse events that occurred

Patient Protection Measures

- Informed consent from the patient or a legal representative;
- Clearance from the institution as specified by its policies;
- Concurrence of the IRB **chairperson**;
- An independent assessment from an uninvolved physician; and
- Authorization from the device manufacturer

What is Compassionate Use?

- **Criteria**
  - Serious disease or condition
  - No alternative treatment exists
  - Sufficient safety/effectiveness evidence
  - Its use should not interfere with the conduct of a clinical trial for the product
- Requires **prior approval** by FDA

Compassionate Use: Request Contents

- Device description
- Description of patient's condition and circumstances necessitating treatment
- Discussion:
  - why alternative therapies are unsatisfactory
  - why probable risk of device use is no greater than probable risk from disease/condition
- **Patient protection measures**

Compassionate Use is about Access

- Normally an unapproved device is only available for clinical study under an IDE
- Compassionate use allows *access* for **treatment**
- Compassionate use is not needed for devices commercially available in the US
  - "practice of medicine"
- Not a substitute for conducting a clinical study/marketing application

Conclusion

- FDA regulates clinical research of investigational medical devices
- Regulations balance the needs to advance research and provide access to novel products while protecting patient safety

Resources

- Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors – Medical Devices

  www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm113709.htm

  – Frequently Asked Questions About Medical Devices
  – Significant Risk and Nonsignificant Risk Medical Device Studies

- Sponsor's Responsibilities For Significant Risk Device Investigations

  www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm049859.htm

Resources

- FDA Guidance: FDA Decisions for IDE Clinical Investigations

  www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279107.pdf

- FDA Guidance: Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with FDA Staff

  www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf

- Device Advice: Expanded Access for Medical Devices

  www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm051345.htm

Questions

Please complete the session survey:

surveymonkey.com/r/DEV-D1S04

Call To Action

- Engage in advancement of novel, innovative medical products that involve clinical research
- Be aware of regulatory responsibilities to advance science and protect patients along the way.