IDE RISK DETERMINATION AND BIMO INSPECTIONS

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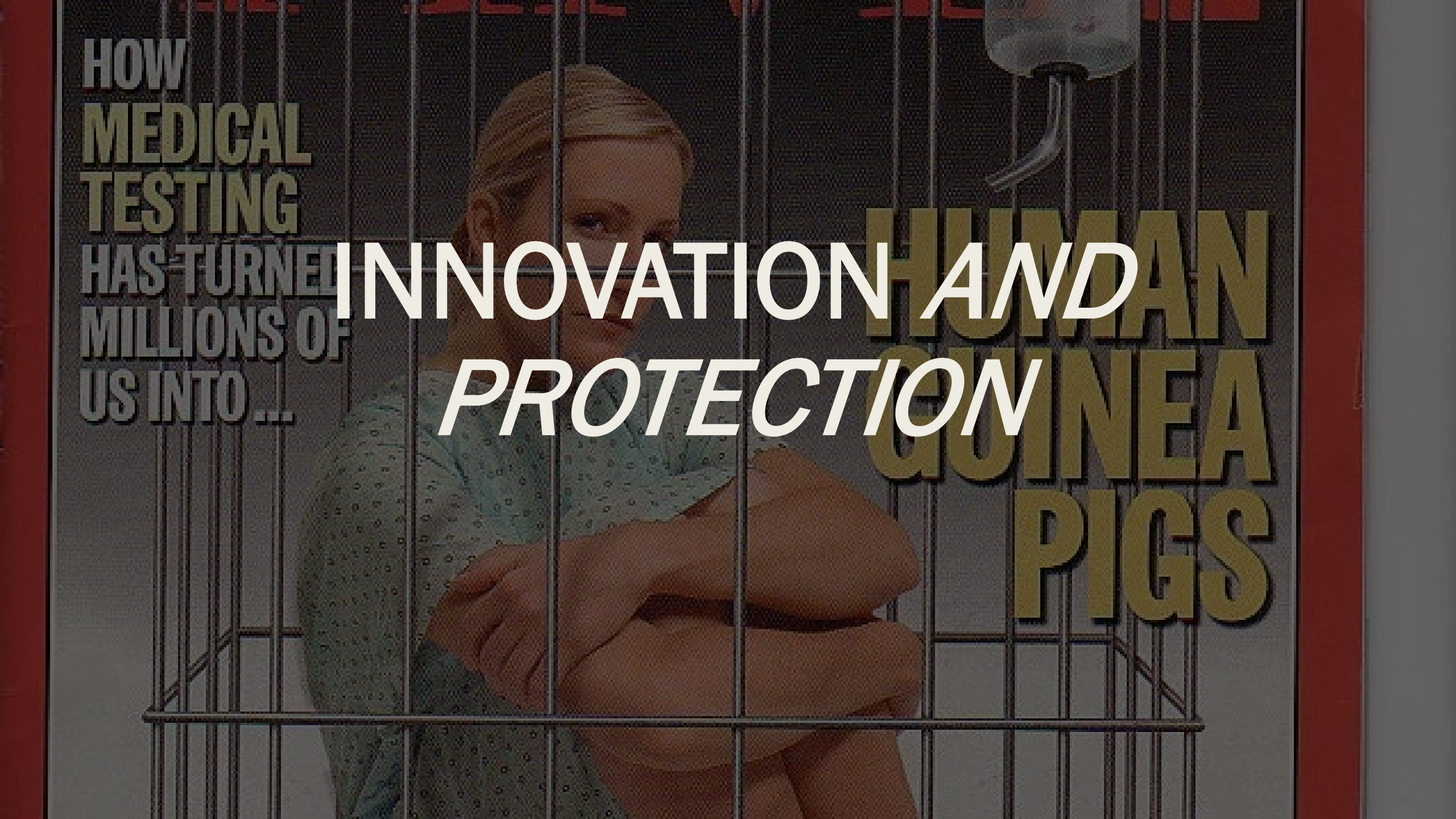
Joint UMSON MRS and B'more SOCRA Chapter Meeting



INNOVATION *AND PROTECTION*

Objectives

- Define Investigational Device Exemption
- Describe the Risk Classification for medical device studies
- Discuss risk determination case study examples
- How to be ready when the FDA is at your door
  - *Sponsor*
  - *Investigator*

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nvestigational Device Exemption

21 CFR 812.1:

*Permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be **shipped lawfully** for the purpose of **conducting investigations** of that device….”*

Regulatory submission that permits clinical investigation of devices

www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-812/subpart-A/section-812.1#

tudies Subject to the Regulation

To gain initial safety and effectiveness information to support further study

To support marketing application [PMA, HDE, 510(k) or *de novo*]

- *New device*
- *New use of legally marketed device ("off-label use")*

Sponsor-investigator studies of unapproved devices or new intended use of approved device (even if no marketing application planned)

hree Types Studies

- Significant risk (SR)
- Nonsignificant risk (NSR)
- Exempt studies

R vs. NSR

Based on risk of use of the device in the study

Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors
Significant Risk and Nonsignificant Risk Medical Device Studies

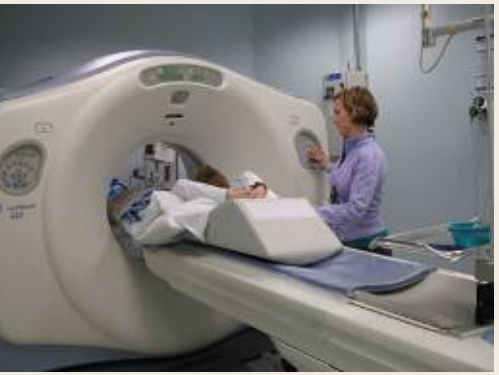
Significant Risk (SR)

- A potential for **serious risk** to the health, safety, or welfare of a subject:
  - (1) implant,
  - (2) supporting or sustaining human life,
  - (3) substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health, **or**
  - (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

21 CFR 812.3(m)

Significant Risk (SR)

- Misdiagnosis and/or error in treatment caused by inaccurate test results would be considered a significant risk.
- Determine treatment, could inaccurate results:
  - *be life-threatening*
  - *result in permanent functional impairment*
  - *result in permanent structural damage*
  - *necessitate medical or surgical intervention to prevent impairment or damage*



Non Significant Risk

- A Non Significant Risk (NSR) study does not meet the definition for a significant risk study.

21 CFR 812.3(m)

Noninvasive

When applied to a diagnostic device or procedure

- Does not by design or intention:
  - Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or
  - Enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os.
- Considered Noninvasive
  - Blood sampling that involves simple venipuncture
  - Use of surplus samples of body fluids or tissues that are left over from samples taken for noninvestigational purposes.

21 CFR 812.3(k)

DE Exempt Studies

- In commercial distribution before May 28, 1976
- Approved/Cleared device that is used or investigated in accordance with the indications in the labeling
- A non-invasive diagnostic device (IVD)
- Consumer preference testing
- Intended solely for veterinary use
- Shipped solely for research on or with laboratory animals and labeled in accordance with *812.5(c)*
- A custom device

21 CFR Part 812.2(c)



Risk Determination

- Is the Device Cleared/Approved?
  - *Is device being used per the indication for use?*
- Proposed use of a device in an investigation, not the device alone.
- Consider the nature of the harm that may result from use of the device.
  - potential harm to subjects:
    - life-threatening
    - could result in permanent impairment of a body function or permanent damage to body structure
    - could necessitate medical or surgical intervention to preclude permanent impairment of a body function
      - *permanent damage to body structure*
      - *undergo a procedure*

NSR Determination

- If the sponsor considers the study is NSR:
  - provide the reviewing IRB an explanation of its determination and any other information that may assist the IRB in evaluating the risk of the study

- Inform the IRB of the FDA's assessment of the device's risk if such an assessment has been made.

RB NSR

- The IRB should ask the sponsor whether other IRBs have reviewed the proposed study and what determination was made.
- The IRB may ask the sponsor for information a description of the device,
  - reports of prior investigations with the device,
  - the proposed investigational plan,
  - a description of patient selection criteria and monitoring procedures,
  - any other information that the IRB deems necessary to make its decision.
- The IRB may also consult with FDA for its opinion.

IRB Decision

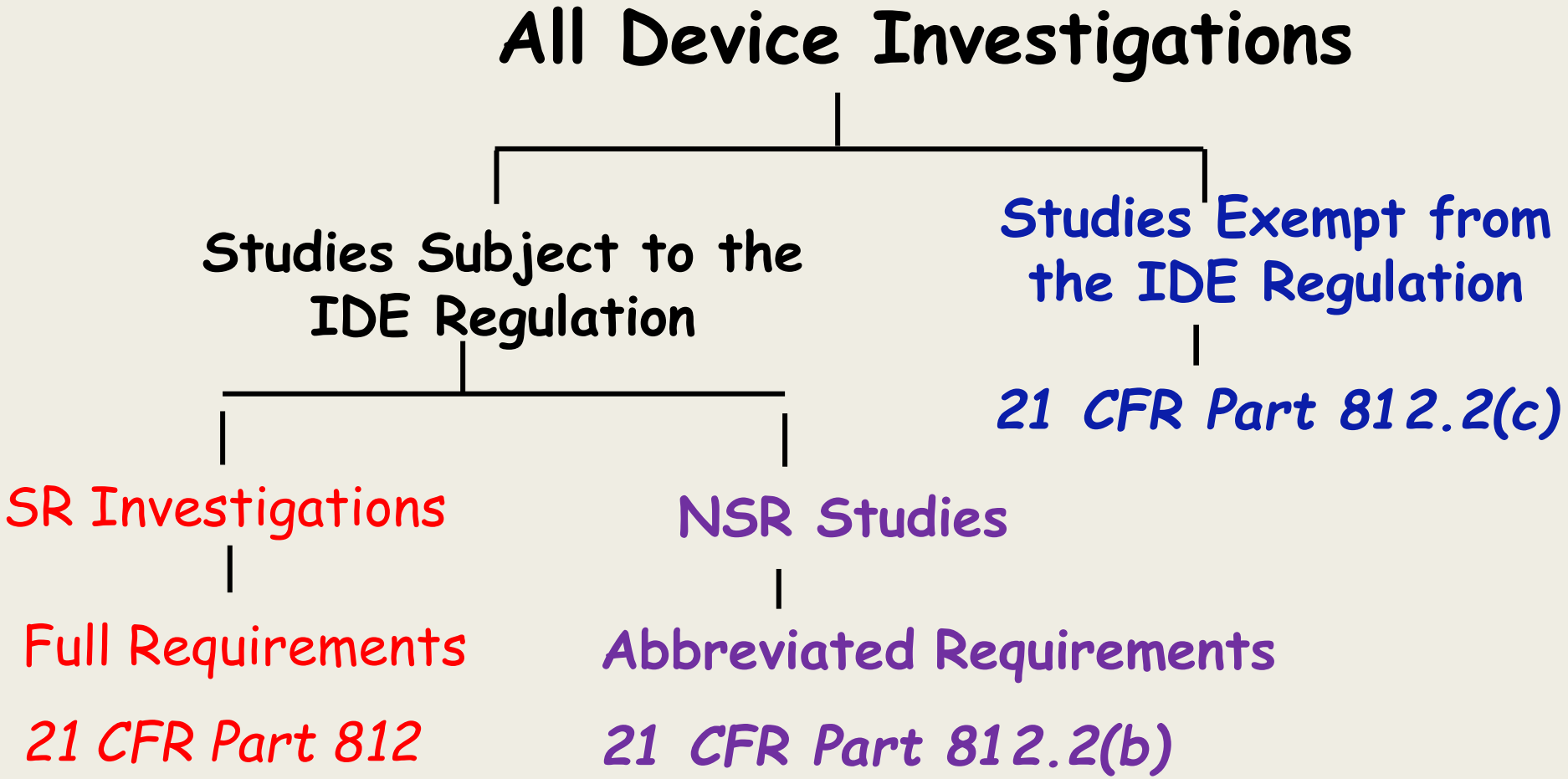
- The IRB may **agree or disagree** with the sponsor's initial NSR assessment.
  - **Agrees and approves** the study, the study may begin without submission of an IDE application to FDA.
  - **Disagrees,** the sponsor must notify FDA that a SR determination has been made. Following FDA approval of an IDE application and IRB approval of the protocol the study can be conducted at that institution as a SR investigation.

Non-Significant Risk (NSR)

- No IDE application to FDA
- Considered to have IDE
- Abbreviated requirements

21 CFR 812.2(b)

SR, NSR, Or Exempt



CASE STUDY

Body Shaping Laser

Body Shaping Laser

Modification to a cleared device

- *New technology- violet laser vs red laser*
- *Increase intensity laser*

Designed for client's seeking noninvasive circumference reduction without invasive surgery.

Allows the patient to continue their daily activities without interruptions from surgery, pain, wounds or garments.

Works by emulsifying adipose tissue which then releases into the interstitial space

Study Design

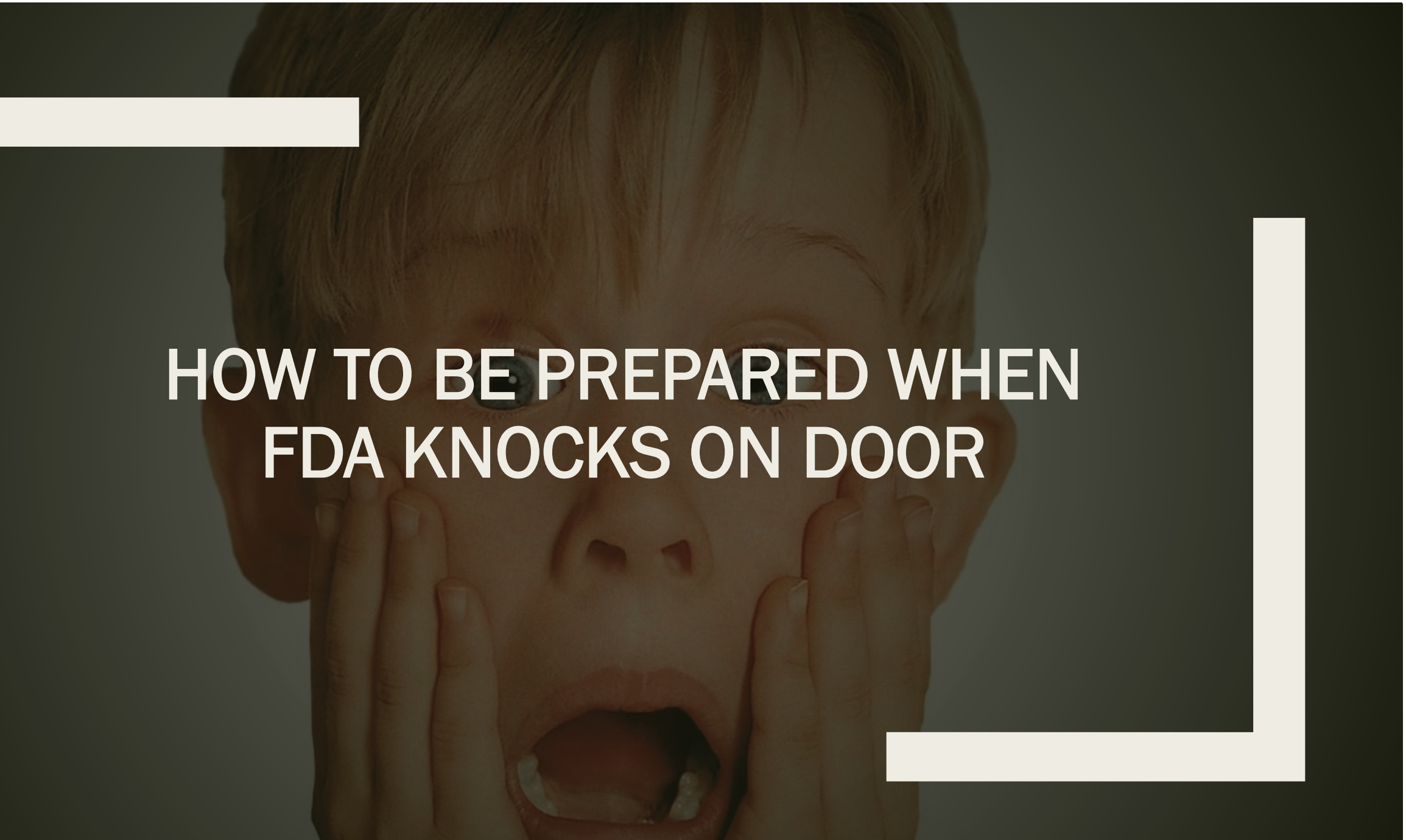
Open-label single-arm design to evaluate the efficacy of application of the Body Shaping OTC violet laser application to that of application of the Body Shaping OTC red laser for the reduction of body circumference.

Risk Determination

- Is the Device Cleared/Approved?
  - *Is device being used per the indication for use?*
- Proposed use of a device in an investigation, not the device alone.
- Consider the nature of the harm that may result from use of the device.
  - potential harm to subjects:
    - life-threatening
    - could result in permanent impairment of a body function or permanent damage to body structure
    - could necessitate medical or surgical intervention to preclude permanent impairment of a body function
      - *permanent damage to body structure*
      - *undergo a procedure*

What is the Risk Determination of the study?

A. *Exempt*
B. *NSR*
C. *SR*



HOW TO BE PREPARED WHEN FDA KNOCKS ON DOOR

Who Does FDA Inspect?

COMPLIANCE PROGRAMS:

CP 7348.811 - Clinical Investigator (CI)

CP 7348.810 - Sponsor/Monitor/CRO

CP 7348.809 - Institutional Review Board (IRB)

CP 7348.808 - Good Laboratory Practices (Nonclinical Laboratories)

Compliance Program Manual

www.fda.gov/ICECI/ComplianceManuals/ComplianceProgramManual/default.htm

FDA Arrival

- Greeting FDA
- Credentials and contact number
- Issue Form FDA 482
  - *Notice of Inspection*
- Initial questions to ask FDA Inspector
  - *Why?*
  - *How long?*

DURING THE INSPECTION

lements of an Inspection

- Interviews with research staff
- Tour
- Review of the written procedures
- Review of records
- Exit interview (Form FDA 483)

During The Inspection

- Have a place for the inspector to review records
- Escort
  - *who?*
- Breaks/lunch
- Responsible person
  - *knowledgeable about the study*
  - *policy on who speaks and answers questions*
- Note taking

During The Inspection

- “War Room”
- Managing copies of documents
- Corrections

Can the FDA request to copy records during an inspection?

A) Yes

B) No

C) It Depends

21 CFR 821.50(b)

(b) Records and information referenced in paragraph (a) of this section **shall be available to FDA personnel for purposes of reviewing, copying, or any other use** related to the enforcement of the act and this part. Records required to be kept by this part shall be kept in a centralized point for each manufacturer or distributor within the United States.

www.ecfr.gov/current/title-21/section-821.50

What FDA Reviews Sponsor/CRO

Protocols (original & revisions)

Signed Investigator Agreements

Sponsor/IRB/FDA/CI Correspondence

Device Distribution Records

- Monitoring Plan
- Training Records
- Case report forms (CRFs)
- Adverse device effect records
- Standard Operating Procedures (SOPs)

hat FDA Reviews Clinical Investigator

Protocol

SOPs

Informed Consent Forms

Case Report Forms

CI Progress Reports

Adverse Effects

- Hospital records
- Radiological Files
- Laboratory Reports
- Device Accountability Records
- Monitoring Logs
- Sponsor/IRB/FDA correspondence

Conclusion of the Inspection

- Closeout discussion with management
- FDA may issue Form FDA 483
  - most responsible person

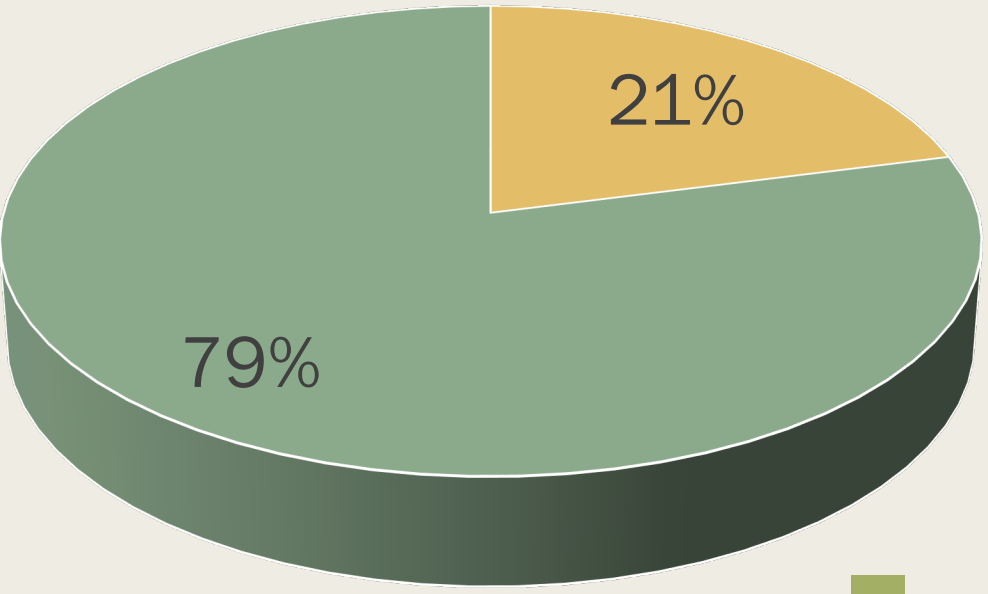
S/M Common Deficiencies

- Failure to secure investigator compliance
- Inadequate Monitoring
- Failure to maintain records
  - Correspondence
  - Device Accountability
  - Signed Investigator Agreements
  - SR/NSR Determination
  - UADE
- Failure to submit annual report IDE
- Failure to submit IDE to FDA

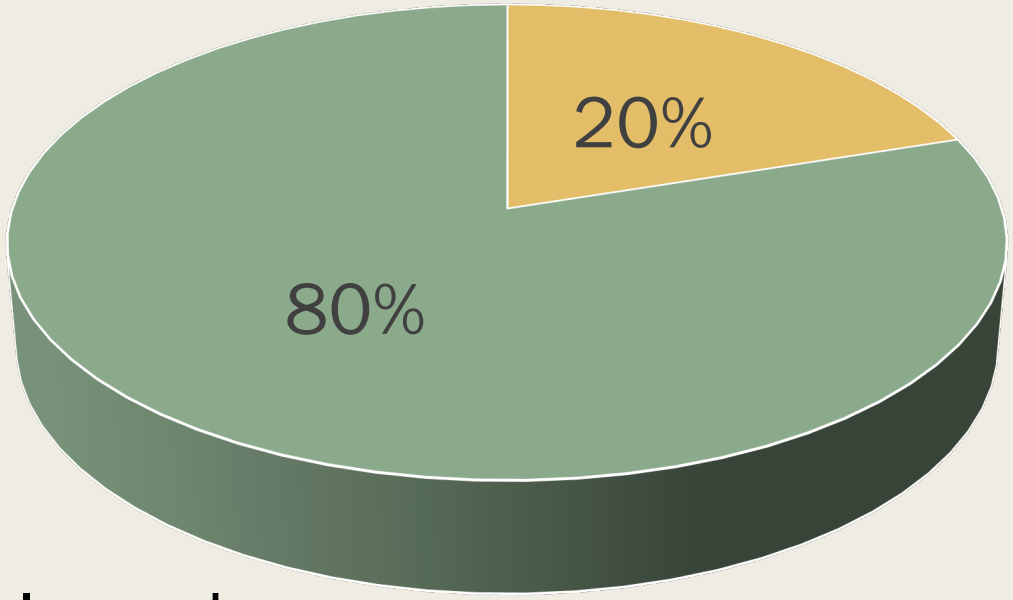
nvestigator Common Deficiencies

- Failure to Follow Protocol
- Inaccurate Case histories
- Failure to Report Adverse Effects
- Failure to Obtain IRB Approval
- Inadequate Product Accountability
- Informed Consent

CI Issued 483



Sponsor Issued 483



No 483 Issued

483 Issued

Response to 483

- Entity may respond in writing **within 15 days**
  - ***not required, strongly suggested***
  - *opportunity to provide clarifications, corrective action, preventive actions, etc.*

xample of Inadequate Response

ailure to adequately supervise the conduct of the study.

esponse: *"I am not, nor ever have been involved with any data ollection or entry in any study. If my life depended on it, I could ot access data. I do not know how. I do not know which atients are enrolled in the current FDA study."*

xample of Inadequate Response

Failure to ensure that the current, IRB-approved version of the nformed consent was executed by each of the subjects in that the 38 unapproved consent forms signed by study subjects were missing basic elements required by regulation to be in an nformed consent document.

Response: *“you cited us on a technicality.”*

BUILD QUALITY INTO DEVICE CLINICAL STUDY:

- From the start
- Every step of process

Steps to Quality Study- Sponsor

- Collaborate, Communicate
- Select Qualified Investigators and Study Sites
- Provide Training
- Adequate Monitoring
- Secure Compliance

21 CFR 812.40

Steps to Quality Study- Investigator

- Follow signed investigator agreement, investigational plan and protocol
- Obtain IRB/IEC approval
- Obtain Informed Consent
- Control investigational devices

21 CFR 812.100

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=812&showFR=1&subpartNode=21:8.0.1.1.9.5

Reporting

Type Report	To FDA	To all Reviewing IRBs	To Other Investigational Sites
nanticipated Adverse Device Effects	X	X	X
ithdrawal of IRB approval	X	X	X
ithdrawal of FDA approval	X	X	X
vestigator List	X		
nnual Progress Report	X	X	X
ecall and Device Disposition	X	X	X
nal Report	X	X	X
se of Device Without Informed Consent	X		
gnificant Risk Determination	X	X	X
rotocol Amendments	X	X	X
rotocol Deviations	X	X	
ther Reports requested by FDA or IRBs	X	X	

Industry Education Resources

Three Resources

CDRH Learn – Multi-Media Industry Education

over 200 modules

videos, audio recordings, power point presentations, software-based "how to" modules

mobile-friendly: access CDRH Learn on your portable devices

http://www.fda.gov/Training/CDRHLearn

Device Advice – Text-Based Education

comprehensive regulatory information on premarket and postmarket topics

www.fda.gov/MedicalDevices/DeviceRegulationandGuidance

Division of Industry and Consumer Education (DICE)

Contact DICE if you have a question

Email: DICE@fda.hhs.gov

Phone: 1(800) 638-2014 or (301) 796-7100 (Hours: 9 am-12:30 pm; 1 pm-4:30pm EST)

Web: www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/ContactUs–DivisionofIndustryandConsumerEducation/default.htm

nspection Resources

Investigator Operations Manual

tps://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-ferences/investigations-operations-manual

FDA Form 483 Frequently Asked Questions

tps://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-ferences/fda-form-483-frequently-asked-questions

FDA Data Dashboard

tps://datadashboard.fda.gov/ora/index.htm

Inspections

tps://datadashboard.fda.gov/ora/cd/inspections.htm

Compliance Actions

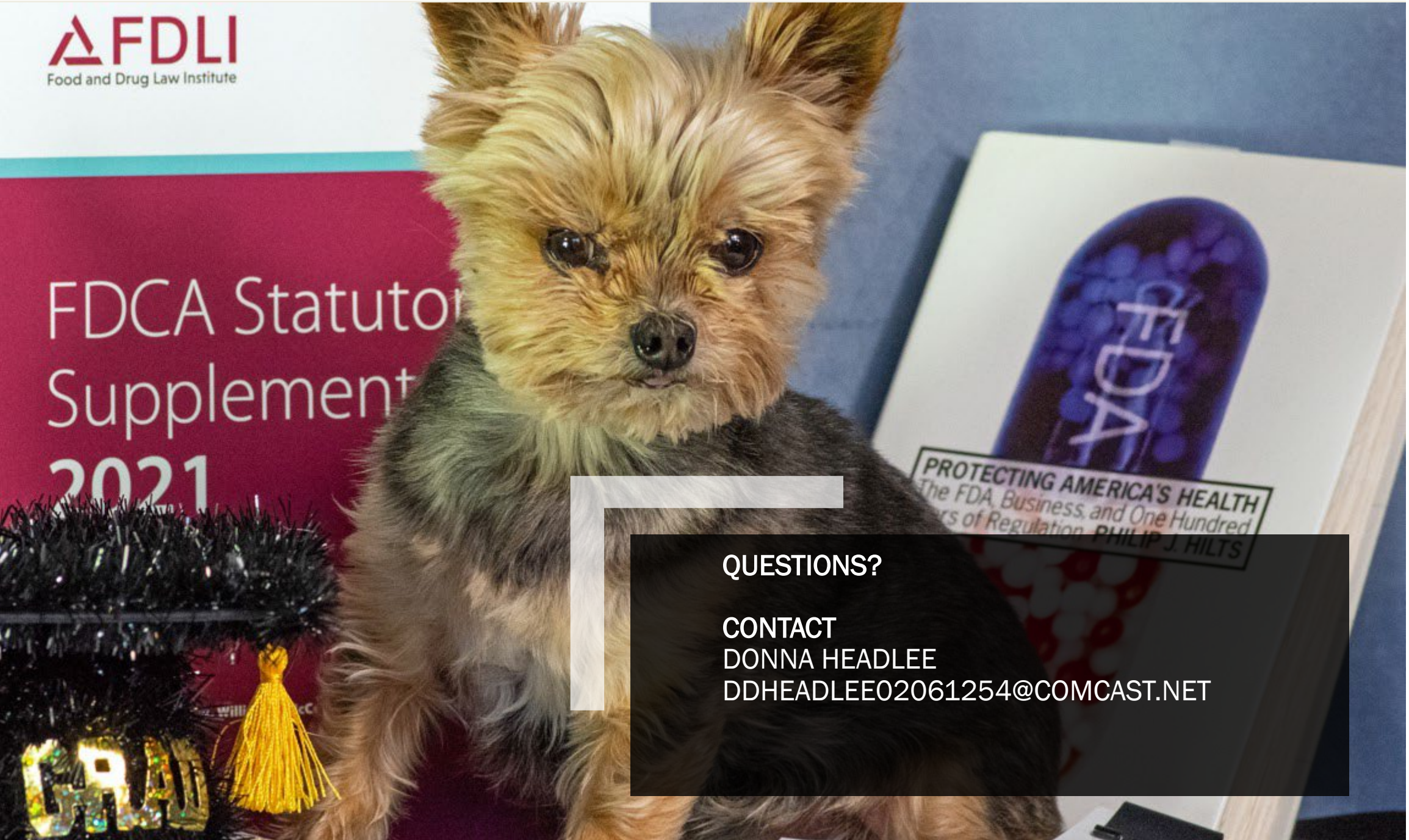
tps://datadashboard.fda.gov/ora/cd/complianceactions.htm

FDA Warning Letters

tps://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-nd-activities/warning-letters

Call to Action

- Consider how device is used in study to make risk determination
- Submit Risk Determination Q Submission
- Comply roles and responsibilities of conducting clinical research
- Build quality into every step of process
- **For questions contact DICE**
  Email: DICE@FDA.HHS.GOV
  Phone: 1(800) 638-2014 or (301) 796-7100
  (Hours: 9 AM-12:30 PM; 1 PM-4:30PM EST)



QUESTIONS?

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