



CLINICAL
TRIALS
TRANSFORMATION
INITIATIVE

How U.S. Regulatory Requirements Contribute to Study Quality

CAPT James Saviola, OD

Director, Division of Bioresearch Monitoring/CDRH

Disclaimer

The views and opinions expressed in this presentation are those of the individual presenter and do not necessarily reflect the views of the Clinical Trials Transformation Initiative or the FDA.

How do U.S. Regulations Contribute to Study Quality?

- *What does “Quality” mean?*
- *FDA BIMO program and Regs.*
- *U.S. Regs. and other “Standards”*
- *“Best Practices”*

Quality

- *The suitability of either a drug substance or a drug product for its intended use.*
- *This term includes such attributes as the identity, strength, and purity (ICH Q6A).*

In Clinical Trials

- *May be defined by the absence of errors that “matter”.*
 - *Impact study endpoints?*
 - *Subject protection?*

Quality by Design (QbD):

A systematic approach to development that

- ***begins with predefined objectives and***
- ***emphasizes product and process understanding and***
- ***process control, based on sound science and quality risk management***

Critical To Quality (CtQ) Factors

- ***Relevant to the integrity and reliability of conclusions based on study data***
- ***To the safety of trial participants***
- ***Trial quality depends on***
 - ***a well-articulated investigational plan***
 - ***clearly defined objectives and associated outcome measures***

<http://www.ctti-clinicaltrials.org/files/documents/QRMworkshop-PrinciplesDoc.pdf>

BIMO Program Objectives

- ***Protect the rights, safety and welfare of subjects in FDA-regulated trials.***
- ***Determine the accuracy and reliability of clinical trial data submitted to FDA in support of research or marketing applications.***
- ***Assess compliance with FDA's regulations governing the conduct of clinical trials, including those for informed consent and ethical review.***

FDA's BIMO Program

- ***A comprehensive, Agency-wide program***
- ***On-site inspections and data audits***
- ***Designed to monitor all aspects of the conduct and reporting of FDA-regulated research***

BIMO Compliance Programs

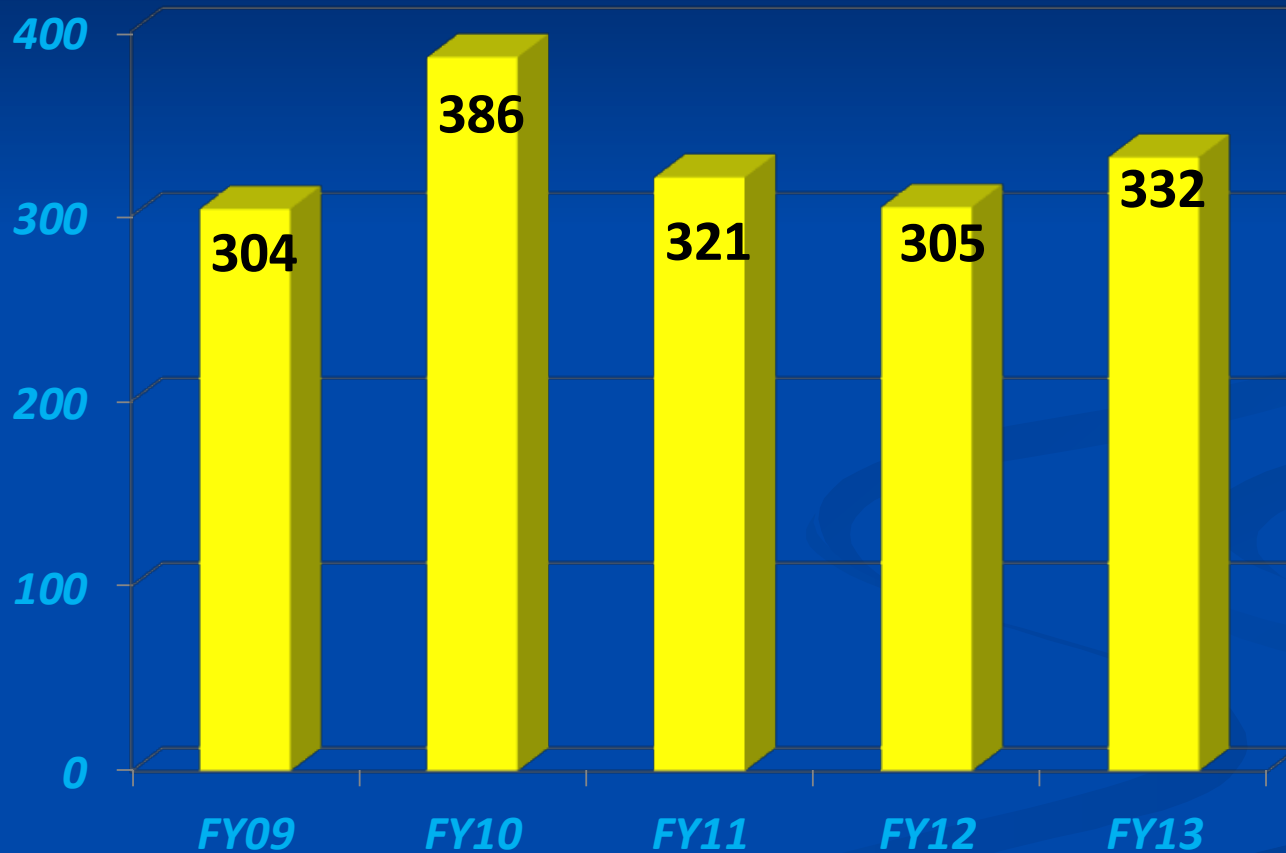
- ***Sponsors, Monitors, and CROs***
- ***Clinical Investigators***
- ***Institutional Review Boards***
- ***Good Laboratory Practices***

CDRH BIMO INSPECTIONS

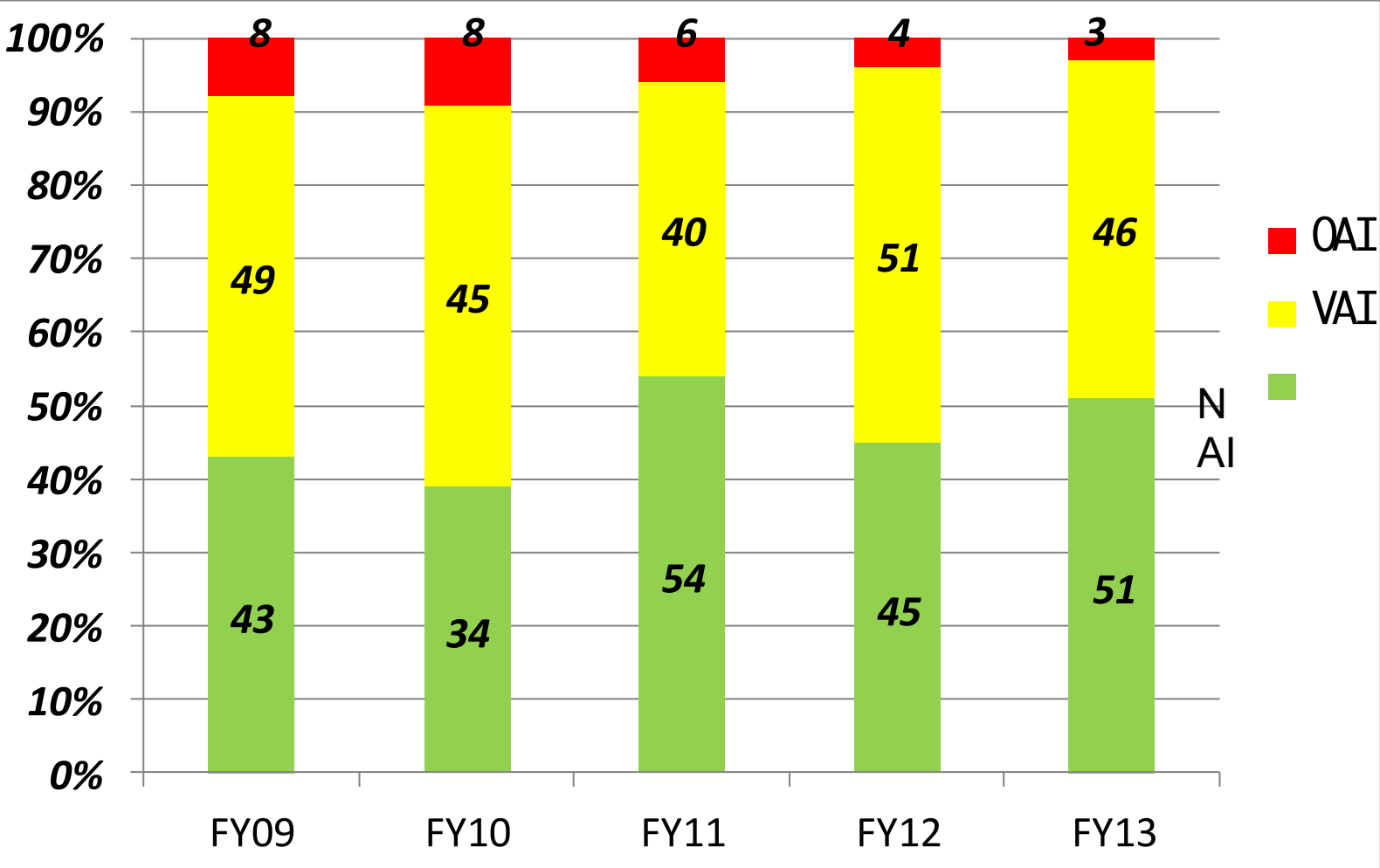
<i>Entity</i>	<i>2009</i>	<i>2010</i>	<i>2011</i>	<i>2012</i>	<i>2013</i>
<i>Sponsor</i>	<i>58</i>	<i>80</i>	<i>62</i>	<i>44</i>	<i>53</i>
<i>CI</i>	<i>163</i>	<i>218</i>	<i>173</i>	<i>194</i>	<i>193</i>
<i>IRB</i>	<i>79</i>	<i>81</i>	<i>78</i>	<i>56</i>	<i>76</i>
<i>GLP</i>	<i>4</i>	<i>7</i>	<i>8</i>	<i>11</i>	<i>10</i>

CDRH BIMO INSPECTIONS

Fiscal Years 2009 - 2013



CDRH BIMO Compliance Rates



Regulatory Similarities across FDA

- ***21 CFR 50: Protection of Human Subjects***
- ***21 CFR 54: Financial Disclosure***
- ***21 CFR 56: Institutional Review Boards***
- ***21 CFR 58: Good Laboratory Practice for Non-clinical Laboratory Studies***

Research Applications

21 CFR

- ***Part 312 Investigational New Drug (IND) application***
 - ***Covers all research (drugs and biologics)***
- ***Part 812 Investigational Device Exemption (IDE)***
 - ***Emphasizes significant risk research***
 - ***Implants, life-supporting, or serious risk***
 - ***Informed Consent Review (812.20(b)(11))***

Significant Risk

IDE required

- ***Intended as implant***
- ***Support or sustain human life***
- ***Substantial importance in diagnosing, curing, mitigating, treating disease or preventing impairment of human health***
- ***Potential of serious risk to health, safety or welfare of subject***

Medical Device Regulations

- ***21 CFR 812: Investigational Device Exemption (IDE)***
- ***21 CFR 814: Premarket Approval (PMA)***
- ***21 CFR 807: Registration/Listing***
 - ***Subpart E- Premarket Notification (510k)***
- ***21 CFR 809: In Vitro Diagnostic Products (IVD)***

Investigational Device Exemption

- ***IDE - 21 CFR Part 812***
- ***Significant Risk (SR)***
 - ***IDE required***
- ***Non-significant Risk (NSR)***
 - ***Abbreviated Requirements***
- ***Exempt from Part 812***

Non-Significant Risk

- ***Based on indication, not just device***
- ***Not Exempt***
- ***Does not meet SR definition***
- ***Abbreviated Requirements of
21 CFR Part 812***

Abbreviated Requirements

Investigator & Sponsor

- ***IRB approval***
 - ***Informed Consent***
 - ***Maintain records***
 - ***Subject's Records***
 - ***Reporting***
 - ***Prohibitions***
 - ***Commercialization***
 - ***Represent as safe or effective while being studied***
- ***Label device***
 - ***Monitoring***
 - ***Maintain records***
 - ***Reporting***
 - ***UADE's***
 - ***Yearly to IRBs***
 - ***Final report to IRB***
 - ***Prohibitions***
 - ***Commercialization***

21 CFR 812.2(b)

Exempt Studies

Exempt from Part 812 but ---

- ***IRB approval***
and
- ***Informed Consent***

--- are still required.

Jan 2012 CtQ Principles

- ***Feasibility***
 - ***Study and Site Feasibility & Accrual***
- ***Protocol Design (8 factors)***
- ***Patient Safety (4 factors)***
- ***Study Conduct (4 factors)***
 - ***Training***
- ***Study Reporting***
- ***Third-Party Service Providers***

**American
National
Standard**

ANSI/AAMI/ISO 14155:2011

**Clinical investigation of medical
devices for human subjects –
Good clinical practice**

**INTERNATIONAL
STANDARD**

**ISO
14155**

Second edition
2011-02-01

**Clinical investigation of medical devices
for human subjects – Good clinical
practice**

*Investigation clinique des dispositifs médicaux pour sujets humains –
Bonnes pratiques cliniques*

ISO 14155:2011(E) Contents

- ***Ethical considerations (7 Elements #)***
- ***Clinical investigation planning (11 #)***
- ***Clinical investigation conduct (11 #)***
- ***Suspension, termination and close-out of the clinical investigation (4 #)***
- ***Responsibilities of the sponsor (4 #)***
- ***Responsibilities of the PI (4 #)***

ISO 14155:2011(E) Annexes

Normative

- ***A - Clinical investigation plan (CIP)***
- ***B - Investigator's brochure (IB)***

Informative

- ***C - Case report forms (CRFs)***
- ***D - Clinical investigation report***
- ***E - Essential clinical investigation documents***
- ***F - Adverse event categorization***

Sponsor

Person, i.e., individual, company, gov't agency, academic institution, private organization, who

- ***Takes responsibility***
- ***Initiates investigation***

21 CFR 812.3(n)

Clinical Investigator

- ***an individual or responsible leader***
- ***actually conducts a clinical investigation***
- ***immediate direction***
- ***test article administer, dispense, or use***
- ***a research subject***

21 CFR 812.3(i)

Sponsor Responsibilities

- *General Duties*
- *Selection of Investigators*
- *Monitoring*
- *Controlling Distribution and Disposition of Devices*
- *Prohibition of Promotion and Other Practices*
- *Supplemental Applications*
- *Maintaining Records*
- *Submitting Reports*
- *Inspections*

21 CFR 812 Subparts C and G

Investigator Responsibilities

- *General Responsibilities*
- *Specific Responsibilities*
- *Maintaining Records*
- *Inspections*
- *Submitting Reports*
- *Device Distribution and Tracking*
- *Prohibition of Promotion and Other Practices*
- *Annual Progress Reports and Final Reports*

21 CFR 812 Subparts E and G

Sponsor-Investigator

- ***Individual, alone or with others***
- ***initiates & actually conducts***
- ***immediate direction***
- ***test article***
- ***administer, dispense, or use***
- ***a research subject***

21 CFR 812.3(o)

Strategies to Conduct a Quality Device Study

- *Select qualified investigators*
 - *“Training and Experience” (21 CFR 812.43(a))*
- *Obtain feedback on protocol requirements*
- *Provide adequate training up front*
 - *Stress importance of informed consent process*
- *Ensure adequate monitoring*
- *Bring investigators into compliance*

Provide Training

Before study & when essential staff replaced

- *Specific study expectations*
- *Procedures unique to the device or its use in the study*
- *Good Clinical Research Practice - !!!*
 - *Regulatory requirements*
 - *Clinician practicing medicine vs. Principal Investigator in a study*

Select Qualified Study Personnel

- ***Clinical Investigators***
- ***Study Coordinators***
- ***Study Monitors***
- ***CROs***
- ***Medical Monitors***
- ***Clinical Project Managers***
- ***Data Managers***

Ensure Monitoring

- ***Early & frequent enough for specific study***
 - ***Early – ensures sites readiness***
 - ***Frequent – catches problems and noncompliance before repetitive***
- ***Systemic issues can be corrected before study integrity is jeopardized***
- ***Regular data audits avoid numerous queries and late database cleanup***
- ***Training opportunity***

Strategies to Conduct a Quality Study

■ *Appropriate Corrective Actions*

- *Determine the source of the problem – root cause***
- *Corrective Action Plan***
- *Update or create standard operating procedures***
- *Train staff***

Take responsibility & rectify issues at the site

■ *Inappropriate Actions*

- *Blaming study personnel or delegates***
- *Simply promising to do better next time***

▶ THANK YOU



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James.Saviola@fda.hhs.gov

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