Consensus Standards

Commonly Used, How to Modify, Statistical Input

AMDM/OIVD Submissions Workshop

Bethesda, MD, April 27, 2011

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Office of *In Vitro* Diagnostic Device Evaluation & Safety (OIVD)

Center for Devices and Radiological Health (CDRH)

Highlights

- Overview - Consensus Standards
- Development - Quest for Standards
- CDRH Standards Recognition
- Commonly Used

General Overview

- Communication methods
- Consumer products
- Travel
- Nutrition
- Physical measurement

Documentary Standards

Use of Consensus Standards

- Codified in P.L. 104-113 “National Technology Transfer and Advancement Act of 1995”
- Interpreted by OMB Circular A-119 (1998)
- Implemented by NIST
  - FDA is a member of the ICSP

Standards Definition

- “The common and repeated use of rules, conditions, guidelines, or characteristics for products or related processes and productions methods, and related management systems practices” (Act)
- “A standard is a document that contains technical specifications or other precise criteria to be used consistently as a rule, guideline, or definition of characteristics, to ensure that materials, products, processes, personnel or services are competent and/or fit for their intended purpose(s)” (NIST)

Types of Standards

- Performance Standard (Horizontal)
- Prescriptive Standard (Vertical)

- Consensus Standard

Quest for Standards

Quest for Standards

American Society for Testing and Materials
International Laboratory Accreditation Cooperation
International Organization for Standardization
International Electrotechnical Commission
National Institute of Standards and Technology
NCCLS-Clinical and Laboratory Standards Institute
Global Harmonization Task Force
American National Standards institute
Institute of Electrical and Electronics Engineers
Association for the Advancement of Medical Instrumentation
World Health Organization
Health Level Seven International

World Health Organization

Bureau International des Poids et Mesures

CLSI

- In 1977, CLSI was first accredited by the American National Standards Institute (ANSI) as a voluntary consensus standards organization. (www.clsi.org)
- CLSI has evolved into a global association of over 1,900 member organizations and over 2,000 experts – working together to improve the quality of medical care

Most commonly used in OIVD

Who Writes the Standards?

- Most standards are actually written by working groups (WG) of experts nominated by their national organizations
  - Technologists
  - Quality Management
  - Clinical Applications
  - MDs
  - PhDs

CLSI Standards Development

- Consensus Committee
  - Chair(s), Members, Advisors, Reviewers
- Document Development Committee
  - Chair(s), Members, Contributors, Secretary
- (Standing) Subcommittee
  - Chair(s), Members, Advisors, Reviewers
- Working Group
  - Chair(s), Members, Advisors, Reviewers, Secretary

Two timelines, 15 and 25-month process

Five voting stages

- Stage 1—Document Development Committee Draft (DDCD) for document development committee approval
- Stage 2—Candidate Draft for Advancement (CDA) for approval by consensus committee and delegates and review and comment by board of directors and the public (nonmembers)
- Stage 3—Consensus Draft (CD) for document development committee approval
- Stage 4—Consensus Draft (CD) for final review and approval by the consensus committee to ensure technical accuracy and overall quality before submission to the board of directors for approval to publish
- Stage 5—Prepublication Draft (PPD) for board of directors' approval to publish

CDRH Standards Recognition

- 510(k), IDE, PMA, HDE, PDP applications
- FDA is authorized to *recognize* all or part of national and international consensus standards through publication of a notice in the *Federal Register*
- Manufacturers may be able to declare conformance to FDA-recognized standards-“Declaration of Conformity”

Conformance can Speed up Premarket Process

- Best:
  - horizontal standards (complete performance standard; clear acceptance criteria)
- Good:
  - vertical standards (study design)
- Then:
  - modifications; non-recognized

More Benefits

- Open communication labs/industry/CDRH
  - consensus decision on challenging issues
- Streamline and improve objectivity of decisions
  - premarket review and compliance inspections

and More

- Less guesswork from industry
- Increased transparency and predictability

Prioritize the role of standards in premarket review as part of the core competency training modules

CDRH Standards Recognition Activities

- 535 committees/subcommittees
- 100+ standards under evaluation at any time
- ~25% of CDRH staff work on standards
- 931 standards recognized to date
  - 371 horizontal; 542 vertical

Recognized Consensus Standards-FDA

Recognized Consensus Standards

CDRH SuperSearch

510(k) | Registration & Listing | Adverse Events | Recalls | PMA | Classification | Standards

CFR Title 21 | Radiation-Emitting Products | X-Ray Assembler | Medsun Reports | CLIA

Search Recognized Consensus Standards

Help | More about Standards

Standards Organization: CLSI - Clinical Laboratory Standards Institute

Type of Standard
(use *ctrl button* with *mouse click* to select up to 3 types, e.g.,*Horizontal, National, Materials Specification*)

- All Standard Types
- Vertical
- Horizontal
- National

Product Area: InVitro Diagnostics

Product Code: | **Regulation Number** (e.g., *888.1111*):

Reference Number: EP

Title or Keywords (30 chars. max):

Publication Date: to

Sort By: Product Area, Item #

for full-text search, select *Go to Simple Search* button

Go to Simple Search | 10 **Records per Report Page** | Search | Clear

Recognized Consensus Standards

510(k) | Registration & Listing | Adverse Events | Recalls | PMA | Classification | Standards
CFR Title 21 | Radiation-Emitting Products | X-Ray Assembler | Medsun Reports | CLIA

10 records meeting your search criteria returned - **Product Area:** *InVitro Diagnostics* ***Clinical Laboratory Standards Institute*** **Reference Number:** *EP*

New Search

Help | More about Standards

Recognition Number	Product Area	Title of Standard	Reference Number and Date	Publication Date	Standards Development Organization
7-110	InVitro	Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline-Second Edition	EP05-A2	10/31/2005	CLSI
7-127	InVitro	Interference Testing in Clinical Chemistry; Approved Guideline - Second Edition	EP07-A2	05/21/2007	CLSI
7-128	InVitro	Evaluation of Matrix Effects; Approved Guideline - Second Edition	EP14-A2	05/21/2007	CLSI
7-143	InVitro	Evaluation of Matrix Effects; Approved Guideline - Second Edition	EP14-A2	09/09/2008	CLSI
7-152	InVitro	User Protocol for Evaluation of Qualitative Test Performance	EP12-A2	09/09/2008	CLSI
7-153	InVitro	User Verification of Performance for Precision and Trueness	EP15-A2	09/09/2008	CLSI
7-174	InVitro	Estimation of Total Analytical Error for Clinical Laboratory Methods; Approved Guideline	EP21-A	03/18/2009	CLSI
7-193	InVitro	Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline	EP6-A	03/18/2009	CLSI
7-194	InVitro	Protocols for Determination of Limits of Detection and Limits of Quantitation	EP17-A	03/18/2009	CLSI
7-212	InVitro	Risk Management Techniques to Identify and Control Laboratory Error Sources; Approved Guideline -	EP18-A2	10/04/2010	CLSI

Recognized Cons

10 records me

ence Number: *EP*

New Sear

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Recognitio Number	Standards evelopment rganization
7-110	CLSI
7-127	CLSI
7-128	CLSI
7-143	CLSI
7-152	CLSI
7-153	CLSI
7-174	CLSI
7-193	CLSI
7-194	CLSI
7-212	CLSI

Recognition List Number: 021 **Publication Date:** 03/18/2009

Part B: SUPPLEMENTARY INFORMATION

Recognition Number 7-193: CLSI EP6-A, Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline. (InVitro Diagnostics)

Date of Standard: 2003.

Address of Standards Organization:

Clinical Laboratory Standards Institute (CLSI)
940 West Valley Road
Suite 1400
Wayne, PA 19087

CDRH Office and Division Associated with Recognized Standards:

OFFICE OF IN VITRO DIAGNOSTIC DEVICE EVALUATION AND SAFETY (*OIVD*)

Devices Affected:

Quantitative In Vitro Diagnostic Devices

Processes Affected:

premarket submissions

Type of Standard:

Horizontal, National

Extent of Recognition:

Complete standard, in accordance with document scope. NOTE: EP6 provides general protocols for establishing linearity in a quantitative in vitro diagnostic assay. users of the protocol should consider the appropriateness of the assumptions of the recommended statistical methods for their particular study results. This guideline does not provide adequate information for whether the established test performance meets regulatory requirements or medical usefulness requirements.

Related CFR Citations and Product Codes:

Consensus Committee on Molecular Methods

MM5-A	Nucleic Acid Amplification Assays for Molecular Hematopathology
MM9-A	Nucleic Acid Sequencing Methods in Diagnostic Laboratory Medicine
MM02-A2	Immunoglobulin and T-Cell Receptor Gene Rearrangement Assays
MM03-A2	Molecular Diagnostic Methods for Infectious Diseases; Approved Guideline
MM13-A	Collection, Transport, Preparation, and Storage of Specimens for Molecular Methods; Approved Guideline
MM18-A	Interpretive Criteria for Identification of Bacteria and Fungi by DNA Target Sequencing

Consensus Committee on Evaluation Protocols

EP05-A2	Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline-Second Edition
EP07-A2	Interference Testing in Clinical Chemistry; Approved Guideline - Second Edition
EP09-A2	Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline - Second Edition
EP14-A2	Evaluation of Matrix Effects; Approved Guideline - Second Edition
EP12-A2	User Protocol for Evaluation of Qualitative Test Performance
EP15-A2	User Verification of Performance for Precision and Trueness
EP21-A	Estimation of Total Analytical Error for Clinical Laboratory Methods; Approved Guideline
EP6-A	Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline
EP17-A	Protocols for Determination of Limits of Detection and Limits of Quantitation
EP18-A2	Risk Management Techniques to Identify and Control Laboratory Error Sources; Approved Guideline - Second Edition

Consensus Committee on Quality Systems and Laboratory Practices

GP10-A	Assessment of the Clinical Accuracy of Laboratory Tests Using Receiver Operating Characteristic (ROC) Plots; Approved Guideline
GP14-A	Labeling of Home-Use In Vitro Testing Products; Approved Guideline
GP20-A2	Fine-Needle Aspiration Biopsy (FNAB) Techniques
GP 27-A2	Using Proficiency Testing to Improve the Clinical Laboratory
GP22-A2	Continuous Quality Improvement: Integrating Five Key Quality System Components; Approved Guideline - Second Edition
GP28-A	Microwave Device Use in the Histology Laboratory; Approved Guideline
GP20-A2	Fine Needle Aspiration Biopsy (FNAB) Techniques; Approved Guideline - Second Edition
GP23-A	Nongynecologic Cytologic Specimens: Collection and Cytopreparatory Techniques; Approved Guideline
GP16-A3	Urinalysis; Approved Guideline

Consensus Committee on Microbiology

M45-A2	Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria; Approved Guideline - Second Edition
M02-A10	Performance Standards for Antimicrobial Disk Susceptibility Tests
M07-A8	Methods for Dilution Antimicrobial Susceptibility Tests of Anaerobic Bacteria That Grow Aerobically; Approved Standard - Eighth Edition
M35-A2	Abbreviated Identification of Bacteria and Yeast
M23-A3	Development of In Vitro Susceptibility Testing Criteria and Quality Control Parameters
M48-A	Laboratory Detection and Identification of Mycobacteria
M27-A3	Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts
M44-A2	Method for Antifungal Disk Diffusion Susceptibility Testing of Yeast; Approved Guideline-Second Edition
M100-S20	Performance Standards for Antimicrobial Susceptibility Testing; Twentieth Informational Supplement
M44-S3	Zone Diameter Interpretive Standards, Corresponding Minimal Inhibitory Concentration (MIC) Interpretive Breakpoints, and Quality Control Limits for Antifungal Disk Diffusion Susceptibility Testing of Yeasts; Third Informational Supplement
M38-A2	Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi
M22-A3	Quality Control for Commercially Prepared Microbiological Culture Media

Consensus Committee on Microbiology

M27-S3	Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts
M34-A	Western Blot Assay for Antibodies to Borrelia burgdorferi
M36-A	Clinical Use and Interpretation of Serologic Tests for Toxoplasma gondii
M40-A	Quality of Microbiological Transport Systems; Approved Standard
M41-A	Viral Culture
M47-A	Principles and Procedures for Blood Cultures
M50-A	Quality Control for Commercial Microbial Identification Systems
M24-A	Susceptibility Testing of Mycobacteria, Nocardiae and other Aerobic Actinomycetes
M6-A2	Protocols for Evaluating Dehydrated Mueller-Hinton Agar
M22-A3	Quality Control for Commercially Prepared Microbiological Culture Media
M28-A2	Procedures for the Recovery and Identification of Parasites from the Intestinal Tract
M11-A7	Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria
M27-A3	Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts

Consensus Committee on Clinical Chemistry and Toxicology

C42-A	Erythrocyte Protoporphyrin Testing; Approved Guideline (1996)
C30-A2	Point-of-Care Blood Glucose Testing in Acute and Chronic Care Facilities
C24-A3	Statistical Quality Control for Quantitative Measurements Procedures: Principles and Definitions; Approved Guideline - Third Edition
C28-A3	Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory
C44-A	Harmonization of Glycohemoglobin Measurements
C28-A3	Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory
C34-A3	Sweat Testing: Sample Testing: Sample Collection and Quantitative Chloride Analysis; Approved Guideline - Third Edition

Consensus Committee on Immunology and Ligand Assay

I/LA23-A	Assessing the Quality of Immunoassay Systems: Radioimmunoassays, and Enzyme, Fluorescence, and Luminescence Immunoassays; Approved Guidelines
I/LA24-A	Fluorescence Calibration and Quantitative Measurement of Fluorescence Intensity; Approved Guideline
I/LA18-A2	Specifications for Immunological Testing for Infectious Diseases
I/LA2-A2	Quality Assurance of Laboratory Tests for Autoantibodies to Nuclear Antigens: (1) Indirect Fluorescence Assay for Microscopy and (2) Microtiter Enzyme Immunoassay Methods; Approved Guideline - Second Edition
I/LA21-A2	Clinical Evaluation of Immunoassays; Approved Guideline - Second Edition
I/LA15-A	Apolipoprotein Immunoassays: Development and Recommended Performance Characteristics; Approved Guideline
I/LA30-A	Immunoassay Interference by Endogenous Antibodies; Approved Guideline
I/LA20-A2	Evaluation Methods and Analytical Performance Characteristics of Immunological Assays for Human Immunoglobulin E (IgE) Antibodies of Defined Allergen Specificities; Approved Guideline - Second Edition

Consensus Committee on Hematology

H15-A3	Reference and Selected Procedures for the Quantitative Determination of Hemoglobin in Blood; Approved Standard - Third Edition
H49-A	Point-of-Care Monitoring of Anticoagulation Therapy; Approved Guideline
H20-A2	Reference Leucocyte Differential Count (Proportional) and Evaluation of Instrumental Methods; Approved Standard - Second Edition
H44-A2	Methods for Reticulocyte Counting (Automated Blood Cell Counters, Flow Cytometry, and Supravital Dyes); Approved Guideline - Second Edition
H11-A4	Procedures for the Collection of Arterial Blood Specimens
H42-A2	Enumeration of Immunologically Defined Cell Populations by Flow Cytometry
H43-A2	Clinical Applications of Flow Cytometry Analysis of Neoplastic Hematolymphoid Cells; Approved Guideline - Second Edition
H21-A5	Collection, Transport, and Processing of Blood Specimens for Testing Plasma-Based Coagulation Assays and Molecular Hemostasis Assays
H56-A	Body Fluid Analysis for Cellular Composition

Going forward

- From CDRH's perspective, standards are an important part of the life cycle of a device and an important tool for protecting and promoting public health

- Deeper engagement in consensus standards for scientific breakthroughs and novel technologies, and to revise currently existing standards introducing more objective metrics for assessing compliance and improving performance

References

- **Guidance for Industry and for FDA Staff: Use of Standards in Substantial Equivalence Determinations (ODE-March 12, 2000**)
  http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073752.htm
- **The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications - Final Guidance (March 20, 1998)**
  http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080187.htm
- **Frequently Asked Questions on Recognition of Consensus Standards (September 17, 2007)**
  http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm074973.htm
- **CDRH Standard Operating Procedures for the Identification and Evaluation of Candidate Consensus Standards for Recognition (September 17, 2007)**
- http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077307.htm
- **FDA Recognized Consensus Standards search (Supplemental Information Sheet (SIS)**
  http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

- **Public law and how government agencies use it:** http://standards.gov

Consensus Standards

Commonly Used, How to Modify, Statistical Input

(part two)

AMDM/OIVD Submissions Workshop

Bethesda, MD, April 27, 2011

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Division of Biostatistics, Office of Surveillance and Biometrics

Center for Devices and Radiological Health (CDRH)

Overview

- Commonly Used Standards (guidelines)
- Issues
  - Modifying Procedures in Guidelines
  - Misinterpretation
- Communication with FDA

CLSI Documents

• Precision		EP5
• Linearity		EP6
• Bias (Trueness)		EP9
• Qualitative Test Performance		EP12
• Limits at Low Levels		EP17
• Total Error (Accuracy)		EP21
• ROC plots	(GP10)	EP24
• Reference Intervals		C28

EP05 Precision

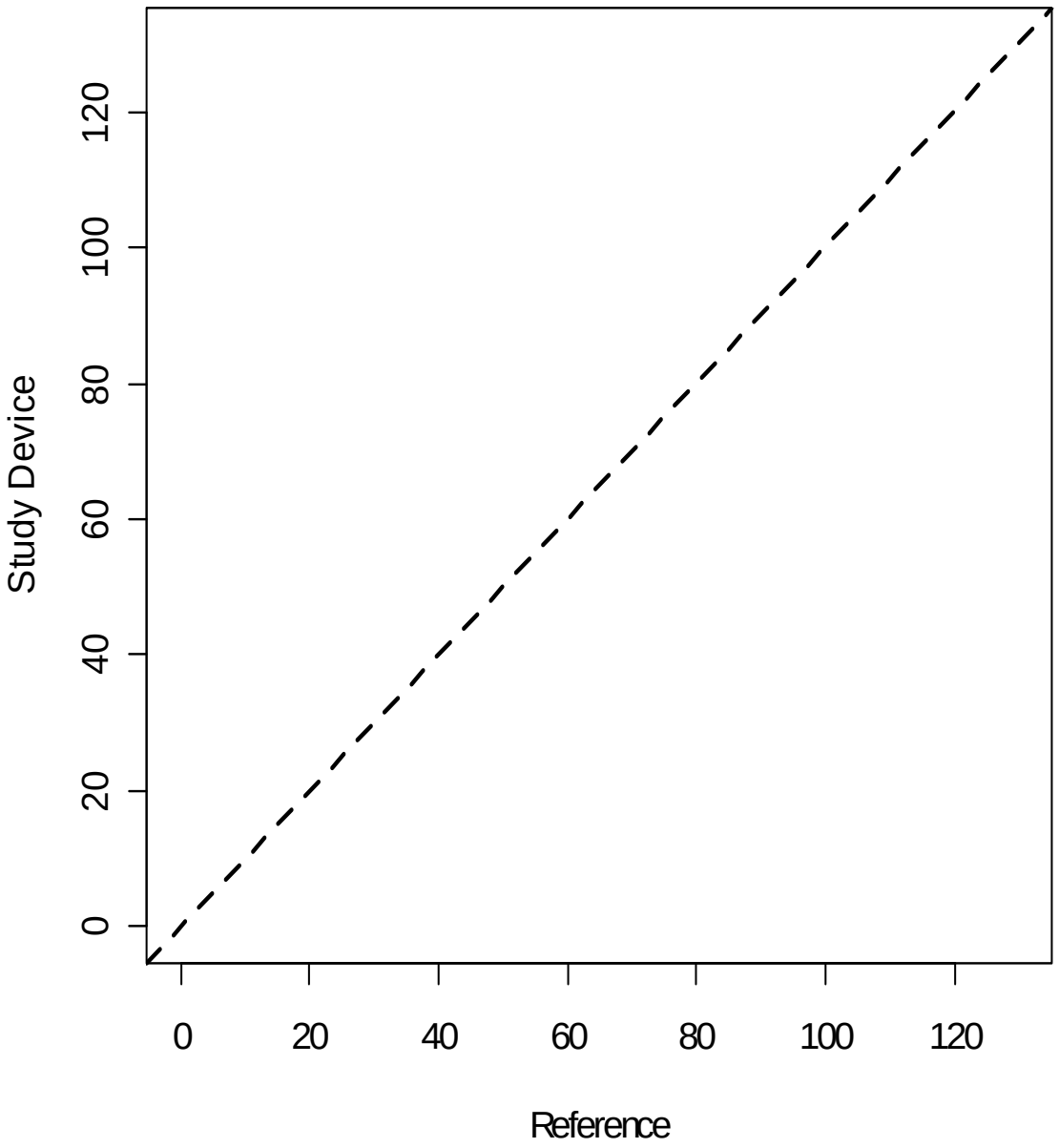
- Evaluate precision performance characteristics: repeatability, reproducibility
  - Manufacturers establish performance
  - Labs can compare to manufacturer's claims

- "Precision estimated via modified EP05"
  - Modification acceptable? ➔ Pre-IDE

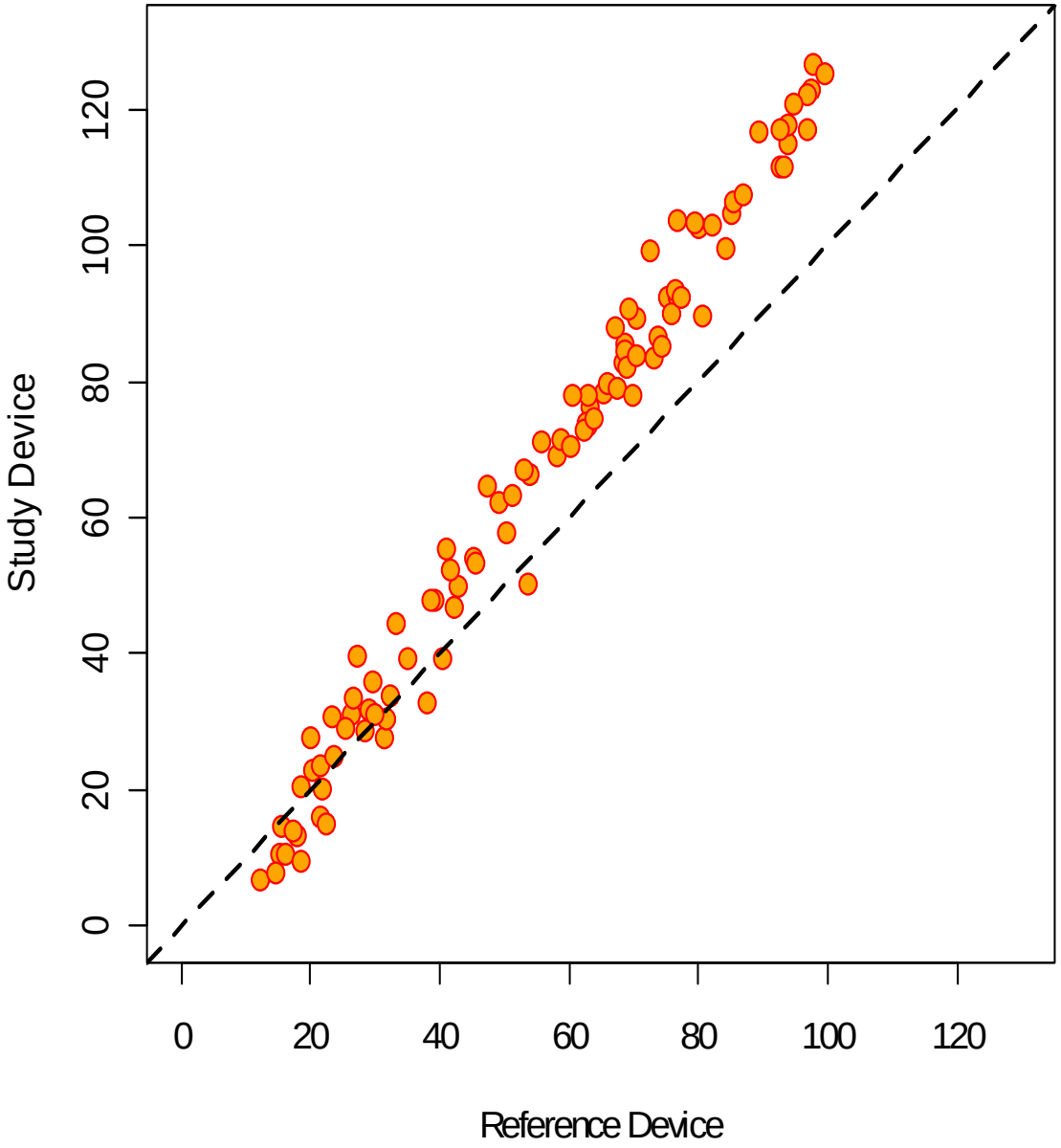
EP09 Bias (Trueness)

- Use regression to estimate bias between study device and reference method at select clinical decision points

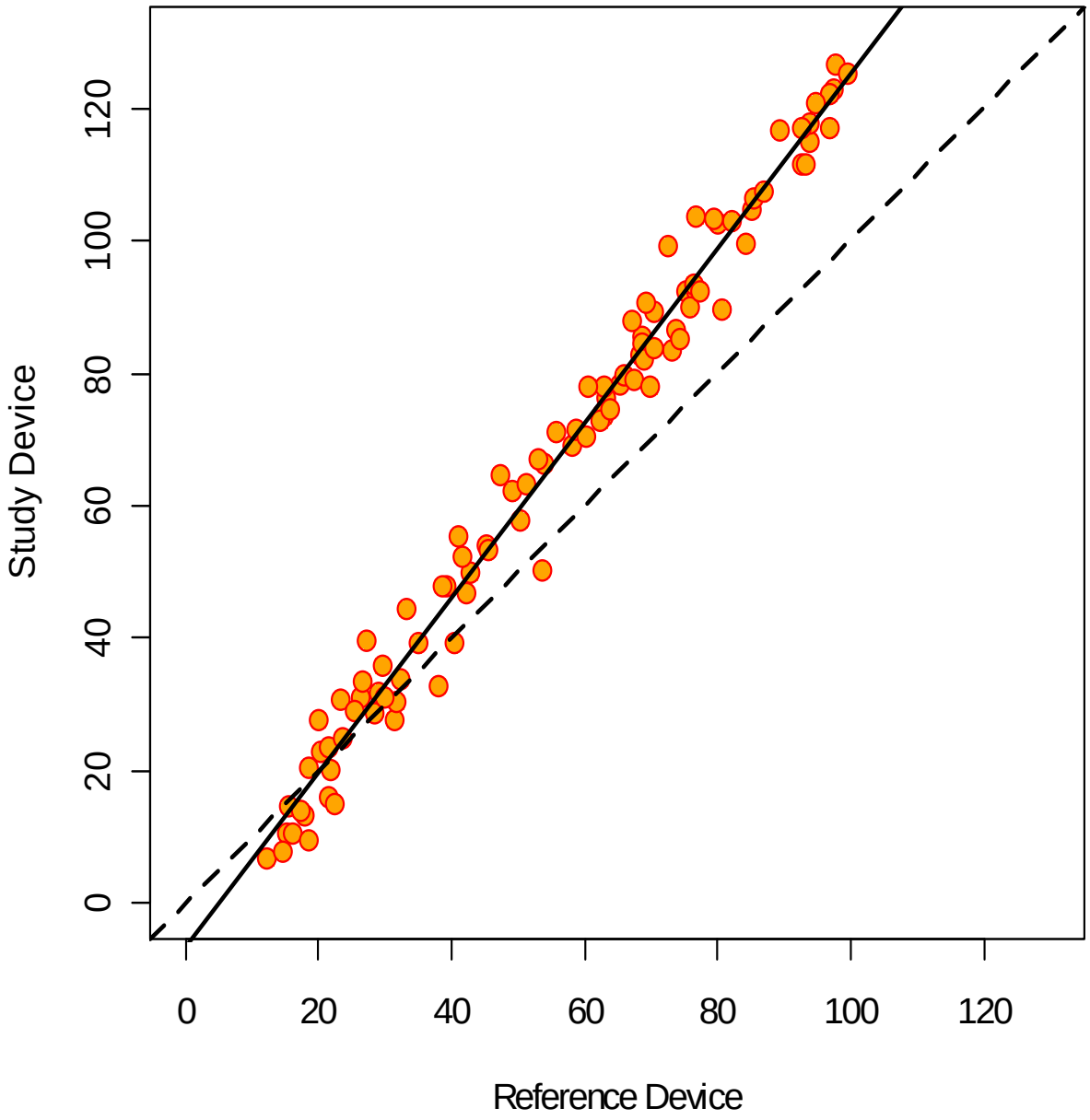
EP 09 (Bias) Example



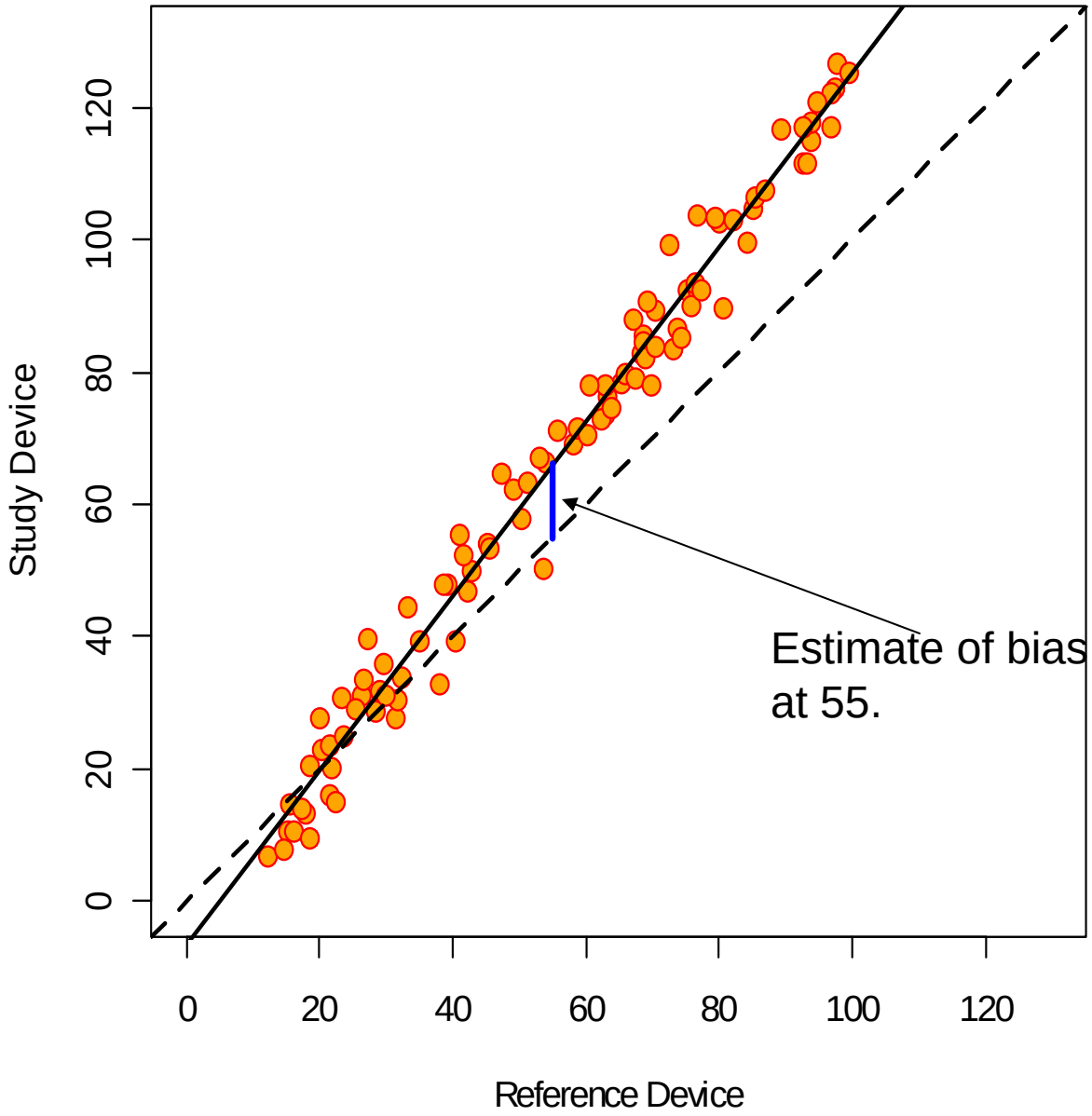
EP 09 (Bias) Example



EP 09 (Bias) Example



EP 09 (Bias) Example

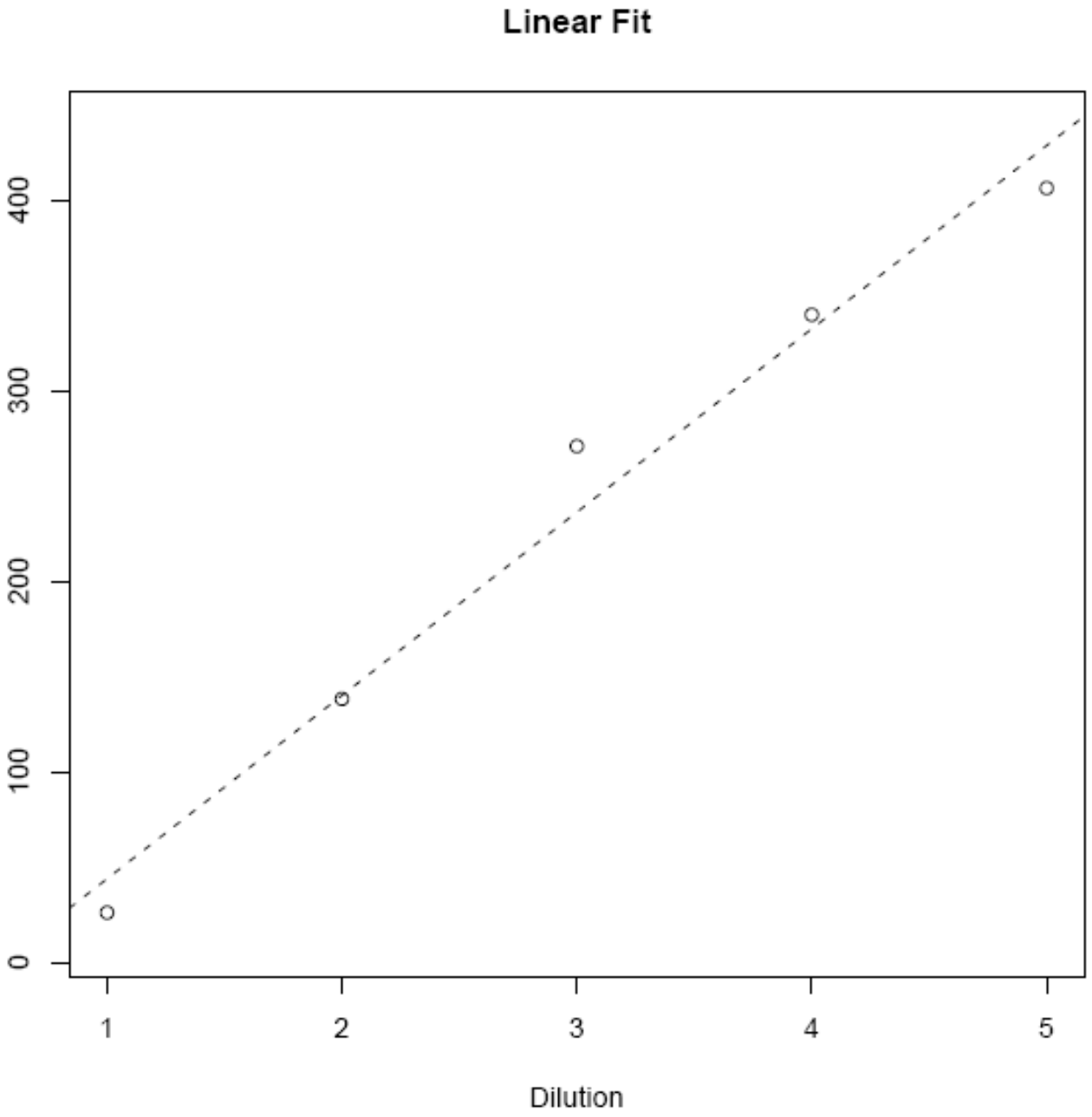


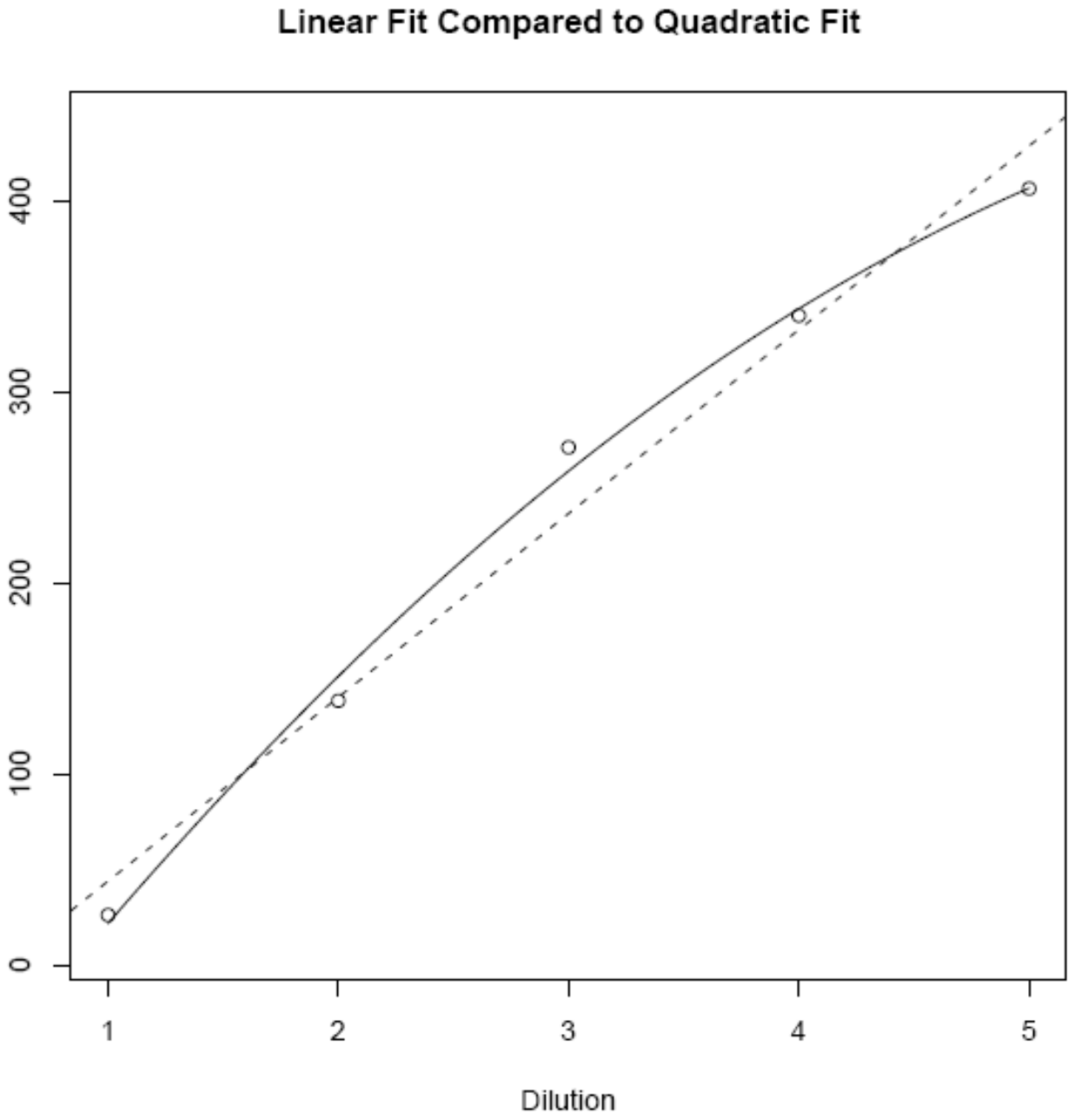
EP09

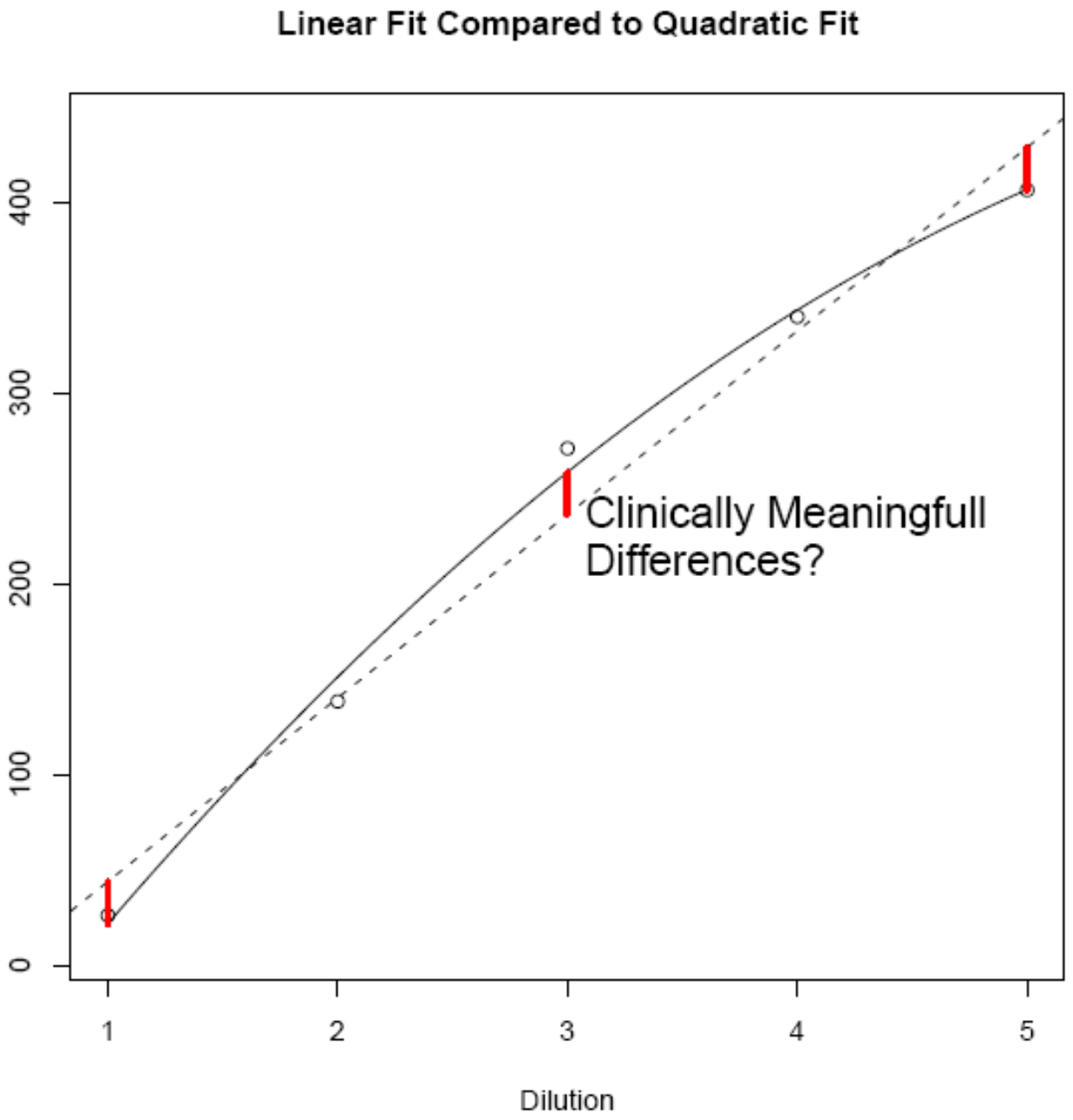
- Sample sizes
  - Labs: 40
  - Manufacturers:100
- Report confidence intervals with estimators
- Questions? ➔ Pre-IDE

EP06 Linearity

- Is assay linear through its range?
- Compares linear fit to polynomial fits.
- Acceptable deviation from linearity is device (use) dependent


Linear Fit
0
100
200
300
400
1
2
3
4
5
Dilution


Linear Fit Compared to Quadratic Fit
0
100
200
300
400
1
2
3
4
5
Dilution


Linear Fit Compared to Quadratic Fit
400
300
200
100
0
1
2
3
4
5
Dilution
Clinically Meaningfull
Differences?

EP 17 Limits at Low Levels

- Limit of Blank (LoB)
- Limit of Detection (LoD)
- Limit of Quantification (LoQ)

EP 12 Qualitative Test Performance

- Qualitative method precision experiment

- Sensitivity & Specificity
  - Dx available
- % Pos Agreement & %Neg Agreement
  - Comparative method

Modifying Standardized Procedures

- Reasonable
- Scientifically valid
- Contact FDA
  - Proper channels
- Pre-IDE process

Outliers
FDA Statistical Perspective

- Observation that “appears” inconsistent with other observations – or are our assumptions about the process wrong?

- Outliers can provide useful information!
  - Report them
  - Provide analyses with and without them

FDA Guidance on Reporting Statistics for Diagnostic Devices

- http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071148.htm

Data and Analyses

- Machine readable
  - Excel
  - SAS
  - .txt
- Include dictionary
  - What are the data?
  - Where did they come from?
- Include confidence intervals

Conclusion

- Standards
- Communication

➔ Efficient Application Review

www.fda.gov/cdrh/oivd

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