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# Clinical Quality By Design: FDA Point of View

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**FDA supports and encourages development of systematic approaches that aim to improve clinical trial quality and efficiency**



# Clinical Trial Quality

- ▶ Scientific question is important; there is a need to produce high-quality evidence to inform decision making on use of a preventive, diagnostic, or therapeutic intervention
- ▶ Trial design is adequate to answer this scientific question; if well conducted the results will be credible
- ▶ Data produced are sufficiently accurate and reliable (fit for purpose) so that they may be used for decision making
- ▶ The rights, safety, and welfare of trial participants have been adequately protected



# FDA Requirements for Clinical Trial Quality

- ▶ 21 CFR 312 broadly describes sponsor responsibilities for clinical trials
  - Selection of qualified investigators
  - Monitoring trial progress
  - Ensuring the trial is conducted according to the investigational plan
  - Review and analysis of accumulating evidence relating to product's safety and effectiveness



# FDA Requirements for Clinical Trial Quality

- ▶ 21 CFR 314.126 broadly describes what constitutes an adequate and well-controlled study\*
  - Study design permits a valid comparison with a control to provide a quantitative assessment of drug effect
  - Method of selection of subjects provides adequate assurance that they have the disease or condition being studied
  - Method of assigning patients to treatment and control groups minimizes bias and assures comparability of the groups
  - Adequate measures are taken to minimize bias
  - Methods of assessment of subjects' response are well-defined and reliable

\* The primary basis for determination of whether “substantial evidence” has been provided to support the claims of effectiveness for new drugs.

# FDA Guidance on “Quality”

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## Guidance for Industry

### Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)  
Center for Devices and Radiological Health (CDRH)  
Office of Good Clinical Practice (OGCP)  
Office of Regulatory Affairs (ORA)  
August 2013  
Procedural

OMB Control No. 0910-0733  
Expiration Date: 03/31/2016  
See additional PRA statement in section VII of this guidance.

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- ▶ Recommends a *quality risk management* approach to clinical trials
- ▶ Protocol be considered blueprint for quality
- ▶ Conduct of a risk assessment to identify and evaluate risks to critical study data and processes
- ▶ Monitoring is one aspect of the processes and procedures needed
- ▶ Monitoring plan be designed to address important and likely risks identified during risk assessment and discourages “One Size Fits All” approach to monitoring

# Addendum to ICH E6

- ▶ Clinical trials have evolved since originally written in scale and complexity
- ▶ New technologies available that when appropriately used permit modernization in clinical trial conduct to better ensure human subject protection and data quality.
  - Clinical trial design
  - Management
  - Oversight
  - Conduct
  - Documentation
  - Reporting
- ▶ Concerns with misinterpretation and implementation in ways that impede innovation

# Goals Addendum to ICH E6

- ▶ Better facilitate broad and consistent international implementation of new methodologies
- ▶ Innovative approaches that emphasize upfront assessment of risks specific to a study design and protocol
  - Quality risk management
  - Quality-by-design processes
- ▶ Discuss other study operational procedures to facilitate innovative approaches, including risk-based monitoring, focusing on critical study elements, and use of technological tools to ensure robust conduct, oversight, and reporting.

# Additional Advice From the Manufacturing Realm...

- ▶ ICH Q9, Quality Risk Management
- ▶ ICH Q10, Pharmaceutical Quality System
- ▶ FDA Guidance for Industry: Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations

***“Quality should be built into the product, and testing alone cannot be relied on to ensure product quality.”***

The clinical corollary...

***Quality should be built into the clinical trial, and audit/inspection (or post hoc rework) cannot be relied on to ensure trial quality***



# Other discussions and guidance on “Quality”

- ▶ Sensible Guidelines for the Conduct of Clinical Trials meetings, 2007-2012
- ▶ EMA, Reflection Paper on Risk Based Quality Management in Clinical Trials, 2013
- ▶ MHLW, Fundamental Notion on Risk Based Monitoring in Clinical Trials, 2013
- ▶ TransCelerate BioPharma, Inc. Risk-Based Monitoring, Quality Management Systems
- ▶ Clinical Trials Transformation Initiatives on Monitoring, Quality by Design, ...



# CTTI Recommendations: Quality by Design

1. **Create a culture that values and rewards critical thinking and open dialogue about quality, and that goes beyond sole reliance on tools and checklists.**

- Consistent with advice in FDA Guidance on Monitoring, which encourages a *quality risk management* approach to clinical trial design and operation, and discourages a one size fits all mentality
- Applicable also to regulatory environments



# CTTI Recommendations: Quality by Design

## 2. Focus effort on activities that are essential to the credibility of the study outcomes.

### Clinical Trial Quality

- ▶ **Scientific question is important; there is a need to produce high-quality evidence to inform decision making on use of a preventive, diagnostic, or therapeutic intervention**
- ▶ **Trial design is adequate to answer this scientific question; if well conducted the results will be credible**
- ▶ Data produced are sufficiently accurate and reliable (fit for purpose) so that they may be used for decision making
- ▶ The rights, safety, or welfare of trial participants have been adequately protected

# CTTI Recommendations: Quality by Design

## 3. Involve the broad range of stakeholders in protocol development and discussions around study quality.

### Clinical Trial Quality

- ▶ Scientific question is important; there is a need to produce high-quality evidence to inform decision making on use of a preventive, diagnostic, or therapeutic intervention
- ▶ **Trial design is adequate to answer this scientific question; if well conducted the results will be credible**
- ▶ Data produced are sufficiently accurate and reliable (fit for purpose) so that they may be used for decision making
- ▶ The rights, safety, or welfare of trial participants have been adequately protected

# CTTI Recommendations: Quality by Design

## 4. Prospectively identify and periodically review the critical to quality factors.

### Clinical Trial Quality

- ▶ Scientific question is important; there is a need to produce high-quality evidence to inform decision making on use of a preventive, diagnostic, or therapeutic intervention
- ▶ Trial design is adequate to answer this scientific question; if well conducted the results will be credible
- ▶ **Data produced are sufficiently accurate and reliable (fit for purpose) so that they may be used for decision making**
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# Few Minutes to Address Regulatory Concerns on Quality Initiatives

1. FDA requires 100% Source Data Verification for monitoring clinical study data. Fact or Fiction?

## Fiction

- 100% Source Data Verification is not an FDA requirement, nor is it specifically recommended in ICH E6
- FDA regulation requires sponsors to monitor trial progress and ensure the trial is conducted according to the investigational plan
- FDA Guidance encourages use of a variety of monitoring techniques as appropriate to meet the needs of the specific clinical trial



# Few Minutes to Address Regulatory Concerns on Quality Initiatives

2. If a clinical site receives a Form FDA 483, then FDA considers data from that site to be unreliable.

## Sometimes, but it depends on...

- Nature of the observation identified on the Form FDA 483
- Extent to which it was found
- Whether it resulted in significant harm to trial participants
- Impact of the observation on critical study data/procedures



# Few Minutes to Address Regulatory Concerns on Quality Initiatives

A related issue ... if a site has received a Form FDA 483, you must not use that site in your clinical trial.

**Your decision...**  
**(unless as a result the investigator  
has been disqualified or is debarred)**

- ▶ Consider:
  - What were the specific observations listed/what was the final classification for the inspection?
  - What impact did observations have on the application (e.g., check Clinical Inspection Summaries)?
  - What corrective actions did the site take in response to observations?



# Few Minutes to Address Regulatory Concerns on Quality Initiatives

3. FDA will issue a Form FDA 483 for issues identified during an inspection that are in areas that we did not consider Critical to Quality.

**Yes that is possible, but please consider...**

- An observation may point to an unanticipated, but critical quality issue.
- Headquarters reviews Form FDA 483s, supporting evidence, and any response of the inspected entity and provides a recommendation to Review Division on data reliability/adequacy of trial participant protections



# Thank You

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***"Quality is never an accident; it is always the result of high intention, sincere effort, intelligent direction and skillful execution; it represents the wise choice of many alternatives"***

***- William A. Foster***

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