



# **Analysis of CDER Bioequivalence Inspections and Findings for 2012**

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# Outline

- Overview of CDER's bioanalytical inspections
- Analysis of Form FDA-483 observations for 2012
- Recent and proposed changes to bioequivalence (BE) investigations program



# Bioanalytical Inspections

## Objectives:

- Evaluate adherence to statutes and regulations
  - ☑ Ensure data quality and integrity
- Examine documentation-Paper and Electronic
  - ☑ Allow reconstruction of the study



# BE inspections (Bioanalytical): Overview

- Facility Tour: Tracking of subject samples
- Equipment and instrumentation
- Procedures (handling of analytical samples)
- Data audit



# Key Elements of BE Inspections (Bioanalytical)

- Storage (freezers, appropriate temp), limited access, monitoring
- Sample handling, chain of custody, extractions, storage, LC-MS/MS system, equilibration samples
- Light sensitivity (if applicable)



# Data Audit

- Assay Validation
- Comparison of data submitted by sponsor in application to source records on site
- Sample reanalysis: Justified? Well documented?



# Data Quality

- QC samples-range covers observed subject concentrations?
- Standard curve-appropriate range
- Run acceptance
- Carryover effect/interference
- ISR



# Data Integrity

- Audit trails-manual integration
- Contemporaneous documentation
- Correspondence File



## Recent Study

- Using internal databases, evaluated Form FDA-483 observations for BE inspections for 2012
- Focus on bioanalytical deficiencies
- Inspection counts were based on the number of applications (NDAs, ANDAs, INDs) inspected



# Objectives

- Determine the total number of inspections conducted/evaluated in 2012 (calendar year)
- Frequency of issuance of Form FDA-483
- Identify common observations for different types of inspections



# Results

Year	Total(%)
2012	180*
Unique Applications	107
ANDAs	64(60)
NDA	41(38)
IND	1
BLA	1
483 Issued	70(39)

\*Using inspection start date



# Results

## Inspections by Type & 483 Issued

<b>Inspection Type</b>	<b>Total (%)</b>	<b>483 Issued/Insp Type</b>
<b>Clinical (Clin)</b>	101(56)	32(32)
<b>Bioanalytical (BA)</b>	71(39)	34(48)
<b>Clin/BA</b>	8(4)	4(50)



## Common Observations: Bioanalytical(By Category)

- Inadequate documentation (most frequent)
- Quality Control (QC)/Calibrators
- SOP Deficiencies
- Manual Integration
- Miscellaneous



# Inadequate Documentation

- Failure to document time QC, calibrator and subject samples were removed and returned to freezers
- Number of times samples were thawed and frozen
- Failure to verify weighing of reference standards by balance printout or initials of witness
- Number of hemolyzed samples not documented on any of the sample transfer forms



## QCs & Calibrators

- Failure to use independent stock solutions for QCs and calibrators
- Freshly prepared QCs and calibrators were not used for stability testing
- Failure to adjust QCs and calibrators for endogenous levels (e.g., testosterone)
- Anti-coagulant in QCs & Calibrators not the same as in subjects samples



# SOP Deficiencies

- SOPs absent or not followed
  - Sample reanalysis
- No SOPs pertaining to computer system/software validation



## Miscellaneous

- Inconsistent manual integration; relatively large number
- Failure to resolve interfering peaks
- Implausible concentrations not investigated
- Failure to report all validation experiments containing valid data



# In Vitro Bioequivalence

- Reserve samples not retained
- A full set of calibrators not used in each run
- cGMP regulations followed, instead of BE
- QCs not used to monitor performance of each run
- Frequency of calibration of instrument not adequate (laser diffraction)



## (BE) Clinical Inspections

- Reserve samples not retained or inadequate number
- Randomization codes for blinded studies not maintained at clinical site
- Failure to maintain complete and accurate case histories
- Informed consent deficiencies: Inadequate information about risk; initiating study prior to obtaining consent from all subjects



# Proposals Under Consideration

- Application-based vs. Surveillance inspections
- Increased collaboration with international regulatory agencies
- Revisiting BE regulations



# Surveillance Inspections

- Development of a surveillance model for BE in addition to application-based inspections
- Use of inspectional elements to derive quantitative measures, improve consistency of inspections, training tool
- Ability to rate inspected entities, and prioritize routine inspections



## FDA/EMA Initiative

- Increased collaboration with EMA in the area of BE inspections
- Sharing of inspectional reports and site information (under confidentiality agreement)
- Conduct joint inspections when needed
- Driven by increased globalization (higher foreign vs. domestic inspections ratio)



# Bioequivalence Regulations

- Regulatory counsels evaluating approaches to update BE regulations
- Depending on availability of resources, may take years

# References



- FDA Regulations – 21 CFR 320
  - Bioavailability and Bioequivalence Requirements
- FDA Guidance document
  - “Bioanalytical Method Validation”
  - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf>
- Compliance Program Guidance Manual
  - In Vivo Bioequivalence Program 7348.001
  - <http://www.fda.gov/downloads/ICECI/EnforcementActions/BioResearchMonitoring/UCM133760.pdf>



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