Bioanalysis in Clinical Trials in China

Current Status and Challenges

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Tow Big Issues for Bioanalysis
Method Validation

• Results from method validation can be used to judge the quality, reliability and consistency of analytical results. Analytical methods need to be validated or revalidated.
Type of Method Validation

Type of validation is indefinite

Full/Partial/Cross-Over Validation

Full/Partial/Cross-Over Validation
Partial Validation

When

Change lab
Change instruments
Change anticoagulant
Change sample preparation method
Change matrix
Change concentration range
Reduce sample volume
Or more ……..

How

Accuracy
Precision
Cross-Over Validation

When

Comparison between labs
Comparison between methods
LC-MS/MS vs. ELISA

Acceptance Criteria

QC: bias ≤ 15%
Subject’s sample:
Bias ≤ 20% in at least 67% of testing sample
Guidance for Method Validation in China

• Pre-1990’s
  ✓ No guidance
  ✓ Variable acceptable criteria for method validation
  ✓ Fully depends on investigator’s knowledge
Guidance for Method Validation in China


ICH Q2A/2B  FDA  SFDA  EMEA
Guidance for Method Validation in China

• GLP Guidance (SFDA, 1999)
• GCP Guidance (SFDA, 2003)

Guidance for Chemical drug clinical pharmacokinetics study
Guidance for Chemical drug bioavailability and bioequivalence study
SFDA, March 2005

Guidance on Bioanalysis: Method validation and analysis of study samples (Draft) 2009

• This is the draft version for the Guidance on Bioanalysis in China Pharmacopeia, 2015 Edition.
• The recommendations are based on the current international guidelines and for adapting the requirements to the development of new drugs and generic drugs.
• It is composed of scope of the guidance, method validation, analysis of study samples, incurred samples reanalysis, ligand binding assays, reports, and definitions.
• Detailed requirements for matrix effect, incurred samples reanalysis, and stability investigation are introduced.

Method Validation

① Specificity/Selectivity
② Calibration Curve/Range
③ Lower Limit of Quantitation, LLOQ
④ Precision and Accuracy
⑤ Stability
⑥ Extraction Recovery

Guidance for Chemical drug clinical pharmacokinetics study
Guidance for Chemical drug bioavailability and bioequivalence study
SFDA, March 2005
Method Validation

⑦ Matrix Effect
⑧ Dilution Integrity
⑨ Carry-over

EMA: Guideline on Validation of Bioanalytical Methods (2012)
AAPS/FDA, EBF, CVG workshop & white paper
Specificity: SFDA, FDA, EMA

At least 6 individual sources of the appropriate blank matrix
Absence of interfering components, such as endogenous substance and its metabolites, is accepted

Similar to SFDA, but more, such as interference from possible co-administered medications
Interference <20% LLOQ

Similar FDA
The possibility of back-conversion of a metabolite into parent analyte
Interference <20% LLOQ
Standard Curve

• Need to report
  ✓ Linearity
  ✓ Coefficient of correlation
  ✓ Accuracy and precision of standard curve samples at each concentration

Acceptance criteria

a) Linearity, \( r \geq 0.990 \)
b) Bias < 15% in more than 75% of standard curve samples
c) Bias < 20% for LLOQ samples
Accuracy and Precision

- **Accuracy**: the degree of closeness of measurements of a quantity to that quantity’s actual (true) value.
- **Precision**: the degree to which repeated measurements under unchanged conditions show the same results, also called reproducibility or repeatability.

Set up concentration level:

QC at low, meddle and high concentration (five samples for each level), three batches

2012-12-3
Stability

Stability in different condition

- Short term
- Stock solution
- Freeze & thaw
- Long term
- Prepared sample
<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-Term</td>
<td>The same duration as the study samples</td>
<td>As FDA</td>
</tr>
<tr>
<td>Short-Term</td>
<td>4-24h based on expectation</td>
<td>Bench-Top</td>
</tr>
<tr>
<td>Freeze-Thaw</td>
<td>Three cycles, 12-24hr/interval, analyze on 3rd cycle</td>
<td>As FDA</td>
</tr>
<tr>
<td>Post-Preparative</td>
<td>Time exceeding the batch size</td>
<td>As FDA</td>
</tr>
<tr>
<td>Stock Solutions</td>
<td>RS and IS</td>
<td>As FDA</td>
</tr>
<tr>
<td>Working solution</td>
<td>Not Required</td>
<td>Required</td>
</tr>
</tbody>
</table>
Extraction Recovery

- **Definition:** The response value from the biological sample divided by the response value from standard sample without matrix at same concentration. ——— SFDA 2005

- **Acceptance criteria:** Similar extraction recovery for LQC, MQC and HQC

<table>
<thead>
<tr>
<th>Nominal Conc.</th>
<th>Extracted QC μg/ml, mean±S.D.</th>
<th>Unextracted standards μg/ml, mean±S.D.</th>
<th>Extraction recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>12.5</td>
<td>11.9±0.5</td>
<td>20.9±0.7</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>40.8±2.1</td>
<td>68.0±1.5</td>
</tr>
</tbody>
</table>

- Definition: The response value from the biological sample divided by the response value from standard sample without matrix at same concentration. ——— SFDA 2005

- Acceptance criteria: Similar extraction recovery for LQC, MQC and HQC
## Carry-Over Test

<table>
<thead>
<tr>
<th>Granisetron</th>
<th>CAL-LLOQ’s (0.1 ng/mL) (peak area)</th>
<th>Carry-over-ULQ’s (10 ng/mL) (peak area)</th>
<th>1st Blank (without I.S.) (peak area)</th>
<th>2nd Blank (without I.S.) (peak area)</th>
<th>3rd Blank (without I.S.) (peak area)</th>
</tr>
</thead>
<tbody>
<tr>
<td>run [#]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4799 (peak area)</td>
<td>415066 (peak area)</td>
<td>650 (peak area)</td>
<td>no peak</td>
<td>no peak</td>
</tr>
<tr>
<td>1</td>
<td>-</td>
<td>425662 (peak area)</td>
<td>657 (peak area)</td>
<td>no peak</td>
<td>no peak</td>
</tr>
<tr>
<td>2</td>
<td>4608 (peak area)</td>
<td>444546 (peak area)</td>
<td>375 (peak area)</td>
<td>no peak</td>
<td>no peak</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>437550 (peak area)</td>
<td>307 (peak area)</td>
<td>no peak</td>
<td>no peak</td>
</tr>
<tr>
<td>3</td>
<td>5698 (peak area)</td>
<td>439028 (peak area)</td>
<td>378 (peak area)</td>
<td>no peak</td>
<td>no peak</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>435957 (peak area)</td>
<td>437 (peak area)</td>
<td>no peak</td>
<td>no peak</td>
</tr>
</tbody>
</table>

**Mean**

- CAL-LLOQ: 5035
- Carry-over-ULQ: 432968
- 1st Blank: 467

**LLOQ/ULQ acceptance**

- Mean "Carry-over-blank’s" (1st, 2nd, 3rd) / Mean LLOQ [%]: 9.3
- Mean Carry-over (1st, 2nd, 3rd) [%]: 0.11

**Note**

- <20% o.k.
Matrix Effect

Required

Recommended

Required

And described how to evaluate in details
Matrix Effect

\[
\text{Matrix Factor} = \frac{\text{Peak response in presence of matrix ions}}{\text{Peak response in absence of matrix ions}}
\]

MF=1: 无基质效应；MF<1，基质（电离）抑制；MF>1，基质（电离）增强
Matrix Effect

Matrix Effect = B/C
Extraction Efficiency = A/B
Incurred Samples Reanalysis (ISR)

Incurred Sample: Subject’s samples
Spiked Sample: Standard cueve samples and QC
Guidance for ISR

- Clinical trials
  - FIH
  - BE
- Sample Selection for ISR
  - Sample around Cmax
  - Sample from terminal phase
  - Sample from different subjects
- Number of ISR samples
  - 10%, if number of total sample <1000
  - 5%, if number of total sample >1000
- Acceptance criteria
  - 67.7% (2/3) of the repeats should be within 20% (30% LBAs) of the reference value
• GLP

GLP, SFDA, 2003

GLP, FDA, 1978

GLP, OECD, 1982

• ISO-17025

Guidance on the Application of Laboratory Competence Accreditation Criteria in the Field of Chemical Testing
Regulatory Guidelines and Documents

- Many more…

- **EFGCP**
  - [Guideline for Auditing Clinical Laboratories](#)
  - 2005

- **PPD**
  - Pharmaceutical Product Development, Inc.
  - Good Clinical Laboratory Practice Standard
  - 2008

- **WHO**
  - Good Clinical Laboratory Practice (GCLP)
  - 2009

- **SFDA**
  - CLINICAL TRIAL BIOANALYTICAL LABORATORY PRACTICE MANAGEMENT, SFDA 2011
Two New Guidelines

• GUIDELINE FOR PHASE I CLINICAL TRIAL, SFDA, Effected on Dec. 02, 2011
  – Based on GCP, and the current situation of domestic Phase I trials
  – Referred to the relevant international regulations.
  – The guideline covers the purpose, foundation and scope of phase I trial. And it,
    • explains the overall requirements for phase I trials.
    • describes the principle of the management of contracts, protocol, subjects, IMP, bioassay of study samples, study data, statistical analysis and final report.
Two New Guidelines

• GUIDELINE FOR CLINICAL TRIAL BIOANALYTICAL LABORATORY PRACTICE MANAGEMENT, SFDA, Effected on Dec. 02, 2011

– to enhance the study quality management of analytical laboratory.
– the main specific requirements were proposed as following:
  • Requirements for organization and personnel
  • Requirements for the facilities of bioanalytical laboratory
  • Emphasizing the management on study quality
1. General Principle
2. Organization and Personnel
3. Lab Facilities
4. Equipments, Materials and Reagents
5. Contract Management
6. SOP
7. Study Conduction
8. Data Management
9. Quality Management
System and Accreditation

- **SFDA Evaluation**
  - Site: >375 hospitals (Specialties >2533)
  - Phase I Unit > 130 units, 8-24 beds per unit

- **CNAS**
  - Many bioassay labs dealing with clinical sample analysis have been evaluated and were issued ISO-17025 certificates by CNAS since 2005.
Summary

• For guideline of method validation, the situation in China is improving.

• Now many Chinese investigators not only follow Chinese guidelines but also consider foreign guidelines in their practice.

• The new guidelines effected last December will have profound influences on the study quality in China.
Acknowledgement

Special thanks for Dr. Hongyun Wang
Mission
China Bioanalysis Forum (CBF)

• Promote the **harmonization** of Chinese regulated bioanalytical guideline with international bioanalytical guidelines

• Promote the **execution** of regulated bioanalysis in China based on the principle of international bioanalytical guidance and industrial best practice

• Actively **participate** the harmonization and globalization of international guidance

• Encourage the **exchange** of academic and industrial research in the field of bioanalysis in China
Steering Committee Members

**Academic**
- Professor Dafang Zhong  
  SIMM
- Professor Hongliang Jiang  
  HUST

**Clinical Research**
- Professor Bei Hu  
  PUMCH Clinical center
- Dr Huichen Liu  
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**CRO**
- Dr Daniel Tang  
  ICON Development Solutions
- Dr Alicia Du  
  Shangpharma

**Pharmaceutical**
- Dr Kelly Dong  
  GSK China
Activities in Plan in 2013

- Provide feedback on FDA new draft guidance on bioanalysis

- Co-sponsor bioanalysis session of CPSA (Chemical & Pharmaceutical Structure Analysis) Shanghai 2013 conference (April 2013)

- Organize 1st CBF symposium (April 2014)

- Participate SFDA organized bioanalytical training for Chinese clinical centers (June 2013)

- Other co-sponsored conferences focused on bioanalysis in China
Thank you for your attention!