China and India Perspective on Global Harmonization of Bioanalytical Guidance

Daniel Tang, PhD/MBA

Shanghai Bioanalytical Discussion Group (SBDG)
Beijing Bioanalytical Discussion Group (BBDG)
Frontage Laboratories (China)

EBF - European Bioanalysis Forum - 3rd Open Symposium
1 - 3 December 2010

上海生物分析研讨会

Acknowledgement

Shrinivas Savale, PhD

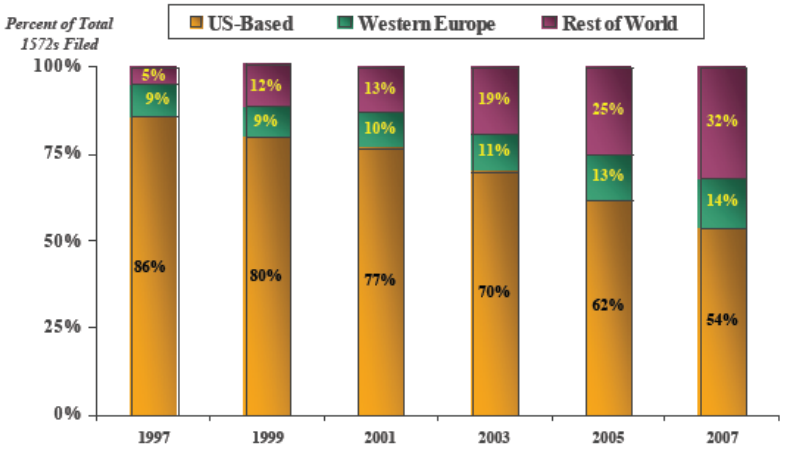
– Bioevaluation Centre, Torrent Research Centre, India

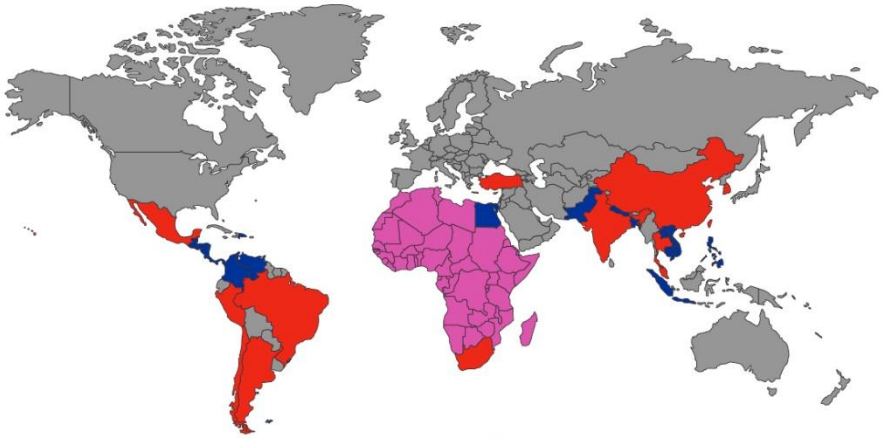
Professor Dafang Zhong

– Shanghai Institute of Materia Medica (SIMM), Chinese Academy of Science, China

Background

- Globalization of clinical trials: more studies conducted outside of US and western EU *
- Regional distribution of Biopharmaceutical Clinical Trials (BCTs)
  - 20% in 2006 for emerging regions
  - 40% in 2010 for emerging regions
  - Average relative annual growth rate in emerging regions is higher
- China and India are playing leading roles in annual growth rate of clinical trials
  - NCE
  - Generic Drug (BE/BA studies)
- High potential of conducting preclinical GLP tox projects in APAC, especially in China





** source: www.clinicaltrials.gov*

Bioanalytical Regulations in APAC

Country	Bioanalytical regulation Status
China	SFDA on non-clinical and clinical development guidelines (2005); Pharmacopoeia of PRC on BA/BE (2010)
India	CDSCO guidelines on BA/BE (2005); Guideline for GCLP (2008); NGCMA GLP Guidance adopted OECD GLP (2002)
South Korean	KFDA Guidance of BE studies (2008)
Australia	TGA Guidance on BA/BE (2002); ARGPM Guideline (2004)
Taiwan	CDE Guidance on BA/BE studies (2006); CDE Guidance on Analytical Method Validation (2000)
Japan	MHLW-NIHS Guidance on Clinical PK Studies (2001); Guideline for BE studies of Generic Products (2006)
Malaysia	MOH Guidelines on BE/BA studies (2000) adopted EMEA principles
Singapore	ASEAN Guidance on BA/BE studies (2004); ASEAN Guidance on Validation of Analytical Procedures (2005)
Thailand	TFDA Guidelines on BA/BE studies (2004)
Saudi Arabia	Saudi FDA BE Requirements Guidelines (2005, following FDA 2001 guidance);

Bioanalytical Regulatory Environment in APAC

- No dedicated guidance on regulated bioanalysis
- No dedicated bioanalytical focused organizations across countries in APAC
- Most of the bioanalytical regulations in APAC follow international guidelines (FDA/EMEA /ICH/MOH)
- Data generated by bioanalytical labs in APAC regions for pre-clinical and clinical development, BE/BA studies will have to face the difficulties of complying with many local and international guidelines.

➡ **There is a great desire for the bioanalytical laboratories in Asia to follow the same harmonized bioanalytical regulation**

Regulated Bioanalysis in China

- Before 1999, bioanalysis rarely followed any international guidelines
- First GLP regulation was issued in 1999 by SFDA
- SFDA guidelines on non-clinical and clinical development were published in 2005
- Pharmacopoeia of PR China introduced guidelines on clinical BA/BE in 2000, which were amended in 2005 and 2010.

→

- None of the guidelines were solely dedicated to bioanalysis, BA guidelines are part of other guidance
- Guidance on bioanalysis was based on 2001 FDA BMV guidance
- Only Chromatography-based methods for small molecules were discussed in detail

Current Status of Regulated Bioanalysis in China

- **Improvements are needed for SFDA guidelines**

- No specific acceptance criteria for some evaluations
  - Specificity, accuracy etc
  - Stability tests
  - Recovery
  - Dilution integrity

- Newest developments are not reflected in SFDA guidelines
  - Matrix effects
  - ISR
  - Partial and cross-validation
  - Repeat analysis including PK

- Interpretation of what is required and putting to practice could be difficult
  - Require clearer guidance
  - Relatively less experience of bioanalytical scientists

Current Status of Regulated Bioanalysis in China

- **The degree of GLP compliance of bioanalytical labs in China varies but has been improving rapidly**

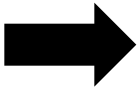
  - Research institutes and clinical centers have accumulated many years' experiences on conducting GLP/GCP studies
  - Global CROs have established their GLP labs in China with same quality systems
  - Many scientists with many years' GLP experience came to China and holding key positions in CROs and Pharmaceutical companies
  - SFDA, instrument vendors and other non-profit organizations offer trainings

- **SFDA has tightened its GLP regulations**

  - Starting from 2005, SFDA conducted on site audits for all nonclinical PK studies for IND application
  - Starting from 2007, SFDA conducted on site audits for all clinical BA/BE studies
  - Currently now GLP certification to Bioanalytical lab

Current Status of Regulated Bioanalysis in India

- Bioanalytical method validation and study sample analysis as a part of BA/BE Guidelines (‘Guidelines for Bioavalability and Bioequivalence’, CDSCO)
- CDSCO (Central Drugs Standard Control Organization, Ministry of Health & Family Welfare) Guidelines for BA/BE studies - March 2005
- NGCMA Guideline (National GLP-compliance Monitoring Authority - established by the Department of Science & Technology, Government of India) adopted OECD GLP - April, 2002.
- Guidelines for Good Clinical Laboratory Practices (GCLP), Indian Council of Medical Research, 2008



- No dedicated guideline for GLP bioanalysis (Method validation and sample analysis)
- Guidelines from different countries are followed to meet respective requirements
- Current guidelines document does not specify chromatography based assays or LBA

Current Status of Regulated Bioanalysis in India

Areas that need update in current guidelines (BA/BE studies, CDSCO 2005) –

- Acceptance criteria and guideline for establishment of following method characteristics -
  - Specificity – including haemolysed and lipemic matrix; rare matrices
  - Stability tests – stock solution, bench-top, long-term, post-preparative,
  - Recovery
  - Dilution integrity
  - Anticoagulant effect
  - Matrix effects
  - Partial and Cross-validation
  - 'Run size' evaluation
  - ISR
- Acceptance criteria and guideline for application of validated method (sample analysis)
  - Batch organization
  - Repeat analysis including PK repeats
  - BMV and sample analysis – differentiation between chromatographic and ligand binding assays (small molecules and large molecules); chiral analysis; multicomponent analysis;

Current Status of Regulated Bioanalysis in India

Regulatory Compliance of bioanalytical labs in India - Encouraging

- Global and national CROs – following GLP principles and having quality systems to ensure compliance with various regulatory requirements
- Vast experience in clinical studies for product registrations across the globe
- Preferred destination for outsourced GLP tox, clinical bioanalysis and clinical research in the world
- Many Indian pharmaceutical companies with global presence bringing in vast regulatory exposure
- GLP certifications for various laboratories – Pharma/Biopharma companies, CROs, National research institutes
- Centre approvals by DCGI (Drug Controller General (India)) for conducting BA/BE studies following GCP and GLP principles
- Monitoring of conduct of clinical development trials from GCP perspective
- Combined initiatives with USFDA, EU and other regulatory agencies to enforce monitoring of various clinical studies across the country

Comparison with Key Guidelines

Topics	China SFDA (current)	FDA (current)	EMA (draft)	India CDSCO (current)
Scope (GLP)	Not defined	Not defined	Method validation should be conducted based on GLP requirement	Not defined
Full/partial validation	Partial validation required when changing species	Partial validation required when changing species	Full validation required when changing species	Not defined (in general method validation is described)
Reference standard /Internal Standard	No requirement for either reference standard and internal standard	Requirement on quality for RS but IS is not specified	Requirement for both RS and IS is specified and stable labeled IS is recommended whenever possible	No requirement for either reference standard and internal standard
Selectivity	Proved from blanks from at least 6 different sources	Proved from blanks from at least 6 different sources	Besides screening 6 different blanks, back-conversion of labile metabolites is specifically discussed	Requirement for number of matrix lots is not defined.
Accuracy	Demonstrated by minimal 3 concentrations and minimum of 5 replicates per concentrations	Demonstrated by minimal 3 concentrations and minimum of 5 replicates per concentrations	Besides requirement of FDA guideline, recommend to demonstrate accuracy of QC samples over at least one run with size equivalent to a prospective analytical run	Demonstrated by minimal 3 concentrations (number of replicates not defined)

Comparison with Key Guidelines

Topics	China SFDA (current)	FDA (current)	EMA (draft)	India CDSCO (current)
Lower limit of quantitation (LLOQ)	At least sufficient to quantify the drug concentrations at 3-5 times of $T_{1/2}$, or 1/10 to 1/20 of C_{max}	At least 5 X the response compared to blank response	No requirement, only with acceptable accuracy and precision	Sufficient to assay the drug/metabolites over the expected concentration range; Intra- and inter-day coefficient of variation usually ≤ 20%.
Precision	Demonstrated by three QC levels (LQC, MQC and HQC) with at least 5 samples per QC level	Demonstrated by three QC levels (LQC, MQC and HQC) with at least 5 samples per QC level	Demonstrated by four QC levels (LLOQ, LQC, MQC and HQC)	Demonstrated at three concentration levels (Low, medium and high) as replicate assays
Calibration curve and dynamic range	• Standards prepared in the same matrix as the samples • ≥ 5 standards in calibration curve • No requirement on the regression model	•Standards prepared in the same matrix as the samples • 6-8 standards in the calibration curve • Use the simplest regression model and selection of weighing. The use of more complex regression needs to be justified	• The freshly prepared stds is recommended in validation • Minimal 6 standards in the calibration curve • No requirements on regression model	**Pre-study phase (Method validation):** • Linear relationships – minimum of 5 standards. • Non-linear relationships - additional points to define the non-linear portions of the curve. **Study phase (Sample analysis):** Estimation of unknowns with concentrations below the LOQ or above the highest standard concentration not recommended;

Comparison with Key Guidelines

Topics	China SFDA (current)	FDA (current)	EMA (draft)	India CDSCO (current)
Carryover	No requirement for assessment	• Carryovershould be assessed and minimized during validation •No acceptance criteria	• Carryover should be assessed and minimized during method development • No acceptance criteria	No requirement for assessment
Stability	• Need to assess but no specific ways to do stability tests • No acceptance criteria is mentioned	•Specific ways to perform stability tests are discussed •No acceptance criteria is mentioned	• Stability in every step during sample prep, analysis and storage need to be evaluated • Stability cannot be proven by literature • Acceptance criteria is ±15% for LQC and HQC • Specify that LTS should be assessed at the same storage temp as samples • Incurred samples should not be used for LTS test	• Stability in the biological matrix under the conditions of the experiment (including any period for which samples are stored before analysis) • Establishment of the absence of any sorption by the sampling containers • Need to assess but no specific ways to do stability tests • No acceptance criteria is mentioned
Recovery	Should be assessed at LQC, MQC and HQC levels	Should be assessed	No requirement	• Assessed at high, mid and low concentrations • low recovery - alternative methods to be investigated • Recovery for internal standard

Comparison with Key Guidelines

Topics	China SFDA (current)	FDA (current)	EMA (draft)	India CDSCO (current)
Dilution integrity	No specific requirement for dilution integrity in method validation	No specific requirement for dilution integrity in method validation	Should be demonstrated with acceptable accuracy and precision	No specific requirement for dilution integrity in method validation
Matrix Effects	Need to assess but no specific ways	• Determining matrix factor (MF) required for 6 individual lots of matrix • <15% variation of MF is required • The requirement of determining MF can be waived if the matrix is rare or stable labeled IS is used in the assay	•Determining MF required for ≥ 6 lots of matrix including haemolysed, hyperlipidaemic and if applicable, from special populations • MF for std and IS should be assessed •The conc. of maximum 3X LLOQ of test compound is specified for MF assessment • If matrix is hard to obtain, matrix effect still need to be assessed	Not defined
Cross-validation	Not specified	No specific procedure and acceptance criteria	• Same set of QCs should be evaluated at different test sites • Diff between test sites should be < 15%	Not specified
Sample analysis	No discussion on incurred sample re-analysis (ISR)	ISR is required for both preclinical tox and clinical studies in 2007 white paper and 2009 AAPS workshop report	• Similar requirement as FDA 2007 white paper • Study samples close to Cmax and in the elimination phase are recommended to be selected for ISR	No discussion on ISR

Recommendations for Harmonization

- Since most of APAC countries are following international guidelines (FDA/EMA/WHO) on regulated bioanalysis, it is important that these guidelines are harmonized in the first place.
- Bioanalytical communities from North America and Europe are likely going to lead the efforts of harmonizing the scientific contents of guidance before sending the recommendations to the regulatory agencies around the world.
- It is important to communicate with scientists and regulatory agencies in APAC countries and get their consensus on accepting the harmonized guidance.
- Bringing all the stakeholders – Pharmaceutical/biotech companies, CROs, Clinical institutes, Regulatory agency – on one platform to address concern on inconsistencies. Efforts must be made to address different applications of bioanalysis.

GBC Initiatives for Harmonization in APAC

- APAC representatives joined Global Bioanalytical Consortium (GBC) Steering Committee (SC)
- CVG Shanghai meeting in Jan 2011: The 1st Asia Pacific Regulated Bioanalysis Workshop
  - It is first time that regulatory agencies and scientific experts from APAC regions to get together and discuss Global harmonization of bioanalysis guidance and GBC
  - Most regulatory agencies from APAC regions in one place ever
- APA India meeting in Feb 2011
- CPSA Shanghai meeting in April 2011