Bioanalytical harmonisation: an European perspective

Olivier Le Blaye, PharmD
French Health Products Safety Agency
Clinical trials inspection unit

EBF, Barcelona, 1 December 2010
Disclaimer

• The views expressed in this presentation are mine and may not represent those of either EMA, the PKWP, or Afssaps

• Discussions between EMA and the FDA take place under confidentiality agreements
Contents

• Harmonisation
  – Guideline / guidance
  – Inspections
The European guideline

• Concept paper published Dec. 2008
  – Main comment received: harmonise with the FDA guideline!

• Work started Sept. 2008

• Draft guideline published Dec. 2009

• End of consultation: 31 May 2010
The European guideline


- Rapporteur: The Netherlands

- Writing Committee:
  - 1 member from The Netherlands
  - 2 members from France
The European guideline

• Based on
  – Crystal City 2006
  – Crystal City 2008 (ISR)
  – Our own experience (problems seen during review of dossiers and inspections)
The European guideline

- New points compared with FDA 2001 Guidance
  - GLP
  - Pre-study validation
    - Matrix effects, carry-over
  - In-study validation
    - Calibration range, QC samples
    - Structure of analytical runs
    - Global precision and accuracy of QC samples
  - Incurred sample reanalysis
The European guideline

• Discussions at several workshops
  – EBF/EUFEPSS Brussels Apr. 2010
  – CVG Montreal Apr. 2010
  – AAPS San Francisco May 2010

• Comments received from > 50 sources
Main points discussed

• Level of detail
  – Too prescriptive, alternative approaches possible
  – Not enough details, tell us how to do
  ➔ ???

• Harmonisation with FDA
  – But what will be in the new FDA guidance?
  – And following some comments would introduce differences
Main points discussed

• Separate and improve LBA section
• Clarify the scope of the document
• Applicability of GLP
  – Clinical trials
  – Pre-study validation
• Full / partial validation (species…)

afssaps
Main points discussed

• Matrix effects
  – haemolysed, hyperlipidaemic samples
  – Excipients in formulations for injection
• QCs: global precision and accuracy
• Incurred sample reanalysis
  – Scope
  – Number of samples
  – Acceptance criteria
• Reporting section
The European guideline

- Next steps
  - Review of comments received (in progress)
  - Incorporate changes in new version (in progress)
  - Further discussions in PK WG
  - Further efforts for harmonisation
Inspections

- Afssaps is the French GLP Monitoring Authority for medicinal products for human use and cosmetics
- Started bioequivalence inspections in 1995, inspections in 23 countries on 5 continents
- Inspections for Afssaps, EMA, WHO
Inspections

• Seen with interest the recent paper by C.T. Viswanathan
  Regulatory observations in bioanalytical determinations
  Bioanalysis (2010) 2 (7), 1325 – 1329

• Similar observations during our inspections, similar conclusions
Inspections

• Calibration range, QC level, LLOQ
  – First discussed during Afssaps inspection in 2005
  – MQC sample: 4 times the highest Cmax
  – LQC: overall CV = 18 % (parent), 28 % (M)
  – LLOQ: 20 % of lowest Cmax (parent), 25 % of lowest Cmax (metabolite)

➤ Trial rejected
Inspections

- **Matrix effects**
  - Often poorly or not studied until 2 – 3 years ago, improving
  - Several cases: systematic difference in IS response between subject samples and calibration / QC samples
    - No investigation of cause and consequences
    - Linked to differences in anticoagulant
    - Poor investigations of matrix effects during method validation

- Trials rejected
Inspections

• Run processing and acceptance criteria
  – Frequent observation: data manipulation
    • Biased re-integrations
    • Improper exclusion of calibration samples
    • Re-injection of calibration / QC samples till run passed, non-used samples not printed and deleted from sequence
    • Concentration of QC samples calculated from calibration curve of another run
**Inspections**

- Run processing and acceptance criteria
  - Frequent observation: data manipulation
    - Affected runs and some trials rejected
    - 3 French tests facilities declared non-GLP compliant in 2006 - 2007, OECD informed, request for data review
Inspections

• Run processing and acceptance criteria
  – Frequent observation since 2003: analytical runs comprised of several batches of samples extracted separately
    • One or several analysts
    • Over one or several days
    • Preparation of fresh solutions, buffers, etc.
    ➢ Heterogeneous conditions
  – Requires acceptance criteria for the whole run but also for each batch of samples
Inspections

• Lack of documentation
  – Preparation of working solutions, spiking of calibration / QC samples
    • Dilutions made ?
    • Pipettes used ?
    • Blank plasma used ?
  – Daily activities
    ➢ Complete reporting ?
  – Audit trail disabled or only partially enabled
Guidelines and inspections

We all have the same ultimate goal: data quality and integrity