Bioanalytical harmonisation: an European perspective

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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

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The European guideline

- Guideline developed by EMA's PK Working Party (former PK subgroup of the Efficacy Working Party), some discussions with Safety Working Party
- Rapporteur: The Netherlands
- Writing Committee:
  - 1 member from The Netherlands
  - 2 members from France

The European guideline

- Based on
  - FDA Guidance for Industry, 2001
  - 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

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The European guideline

- Discussions at several workshops
  - EBF Barcelona Dec. 2009
  - EBF/EUFEPS Brussels Apr. 2010
  - CVG Montreal Apr. 2010
  - AAPS San Francisco May 2010
- Comments received from > 50 sources

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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

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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…)

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

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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

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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

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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