Regulatory Demands for Biostudies

Recap of Presentation № 1

- Design should allow accurate assessment of the treatment effect
- Highest sensitivity to detect differences between formulations considered for/in
  - highest dose strength (generally)
  - single dose
  - fasting state
- Appropriate sample size (80 – 90% power) and design
- Assessment
  - Inclusion the 90% confidence interval within the BE-limits 80.00 – 125.00%
    - Wider BE-limits for HVD(P)s
    - Narrower BE-limits for NTIDs

Sample Size (more in Presentation № 4)

- Minimum Sample Size
  - 12 WHO, EU, CAN, USA, AUS, NZ, AR, MZ, ASEAN States, RSA, Russia (‘Red Book’), EEU, Ukraine
    USA ‘A pilot study that documents BE can be appropriate, provided its design and execution are suitable and a sufficient number of subjects (*e.g.*, 12) have completed the study.’
  - 18 Russia (2008)
  - 20 South Africa (modified release formulations)
  - 24 Saudia Arabia (12 to 24 if statistically justifiable), Brazil, USA (replicate designs intended for RSABE), EU (TRT|RTR replicate designs intended for ABEL)
  - ‘Adequate’ India, ‘sufficient number’ Japan

Sample Size (more in Presentation № 4)

- Maximum Sample Size
  - Not mentioned in any guideline
  - Decided by the IEC/IRB and/or local authority
  - An extremely high sample size – if the sponsor can afford that – might give the impression of ‘overpowering’ the study
    - The width of the confidence interval (for a given variability) depends on the sample size
    - A high sample size (say, planned for >90% power) leads to a narrow CI which will give a passing study even if the deviation of test from reference is high
    - Has lead to rejection of protocols in the past
    - However, once a protcol is approved and the study performed, there is no reason for an agency to reject the study → the patient’s risk is not affected and still 5%

GCP issues (more in Presentation № 7)

- Manufacturing of investigational products according to the rules of cGMP
- Study scientically justified
  - Design (BE-limits, sample size, statistical methods)
  - Validated bioanalytical method (more in Presentation № 5)
  - Ethical issues
    - Potential benefit for patients outweighs risk of study participants
    - Informed consent form and procedures ready
- Study protocol
  - Approved by IEC/IRB
  - Approved by agency (if applicable)

GCP issues

- Study Initiation
  - Recruitment of volunteers
  - Obtain informed consent
  - Perform pre-study exams
  - Recommended
    - More eligible subjects should be invited for the first administration than the required sample size dictates
      - Subjects might get ill after the pre-study exam or withdraw consent
      - These subjects are called ‘stand-ins’ and will be included only if necessary

GCP issues

- Study Performance (Clinical Part)
  - Hospitalization the evening before administrations in all periods (otherwise, the mandatory fasting period of ten hours is not guaranteed)
  - Basic vital signs (blood pressure, heart rate) within one hour before administrations
  - Administration according to the study protocol, *e.g.*,
    - Volume of water
      (at least 150 mL, non-carbonated, ambient temperature)
    - Upright position
    - Extreme physical restrictions (*e.g.*, lying on the right side for two hours, lying for another two hours, then sitting) are generally counterproductive

GCP issues

- Study Performance (Clinical Part)
  - Blood sampling as planned
    - Samples on ice and/or stabilization, maximum interval until centrifugation, centrifugational force and duration, aliquotation of plasma samples, temperature of freezer)
  - Interim safety measurements (if applicable) and recording of Aes
  - Standardized food/beverages at defined times
    - Generally water can be consumed starting one hour after administration but should not exceed three liters per day
  - In each study period a short physical exam before check-out
  - At the end of the study (within four days after check-out) the same parameters like in the pre-study exam should be measured
  - Sample shipment to the bioanalytical site

GCP issues

- Study Performance (Clinical Part)
  - All performed steps should be documented in the Case Report Form (CRF) in a timely manner
  - Erroneous entries should be corrected in such a way that the original entry is legible
  - Lab exams, radiographs, etc. should be attached to the CRF
  - Activities not directly related to subjects (*e.g.*, receipt and storage of formulations, record of the freezer's temperature, sample shipment) should be documented and kept in the study file

GCP issues

- Study Performance (Bioanalytical Part)
  - Validated Method (more in Presentation № 5)
  - All steps should follow the Bioanalytical Protocol
    - Blinded for treatment (*i.e.*, only subject / period / scheduled sampling time known to the bioanalyst)
    - Documentation of
      - receipt of samples from the clinical site
      - storage of samples (duration, temperature)
      - preparation of stock solutions for calibrators and QC samples
      - preparation af calibrators, QCs, sample preparation
      - analytical batches, calculation of concentrations
      - incurred sample reanalysis
  - All results compiled in the Bioanalytical Report
  - Transfer of results to biostatistics

GCP issues

- Study Performance (Biostatistical Part)
  - Statistical Analysis Protocol in place (more in Presentation № 6)
  - All steps should follow the SAP
    - Documentation of
      - receipt of blinded data from the bioanalytical site
      - NCA to calculate PK metrics of interest
      - locking the database
      - unblinding the study with the randomization scheme (from the clinicial site ot the sponsor)
      - statistical evaluation and assessment for BE (in a two-stage design: estimate the sample size for the second part)
  - All results compiled in the Biostatistical Report
  - Transfer of results to medical writing

GCP issues

- Study Performance (Medical Writing)
  - Compile clinical, bioanalytical, and biostatistical results
  - Clinical Study Report according to ICH E3 (1995)
    - Not all parts of ICH E3 are applicable to a BE study
    - Remove parts (*e.g.*, dealing with efficacy) and reorder as necessary Examples given in ICH Q&A R1 (2012)
    - Give relevant parts of the bioanalytical and biostatistical reports already in the main text
    - Appendices (at least)
      - Study protocol(s) and amendments (if applicable)
      - Positive vote of the IEC/IRB
      - CVs of PI and sub-investigators
      - Documentation of cGMP conformity of IMPs, receipt, storage
      - Documentation of sample storage, shipment
      - Complete bioanalytical and biostatistical reports

PK Metrics of Interest (details in Presentation № 6)

- Single Dose Studies
  - C_{max} Highest observed concentration within the profile
  - t_{max} Time point of C_{max}
  - AUC_{0-t} Area under the concentration-time curve from the time of administration to the time point of the last measured concentration
  - $AUC_{0-\infty}$ AUC extrapolated to infinite time
  - For immediate release products *instead* of AUC_{0-t} and $AUC_{0-\infty}$
    - AUC_{0-72} AUC truncated at 72 hours
  - Most controlled release products show – by design – 'flip-flop' pharmacokinetics (*i.e.*, $k_a \leq k_{el}$)
    - The late phase of the profile represents absorption
    - Sample long enough to get a reliable $AUC_{0-\infty}$

PK Metrics of Interest (details in Presentation № 6)

- Multiple Dose Studies
  - $C_{max,ss}$ Highest observed concentration within the profile
  - $t_{max,ss}$ Time point of $C_{max,ss}$
  - $AUC_{0-\tau}$ Area under the concentration-time curve from the time of administration to the end of the dosing interval (τ)
  - Innovators / originators
    - $C_{min,ss}$ Lowest observed concentration within the profile
  - Generics
    - $C_{\tau,ss}$ Concentration at the end of the dosing interval

Assessment of BE Studies

- The authority should be provided with
  - Study Synopis giving a brief overview of procedures and results (less than ten pages)
  - All information pertinent to GCP compliance
    - Study Protocol (and amendment(s), if applicable)
    - IEC/IRB approval
    - Documentation of IMP manufacturing, shipment, storage
    - Case Report Forms
    - At least 20% of chromatograms
      (all should be readily available upon request)
    - Study Report including all appendices

Assessment of BE Studies

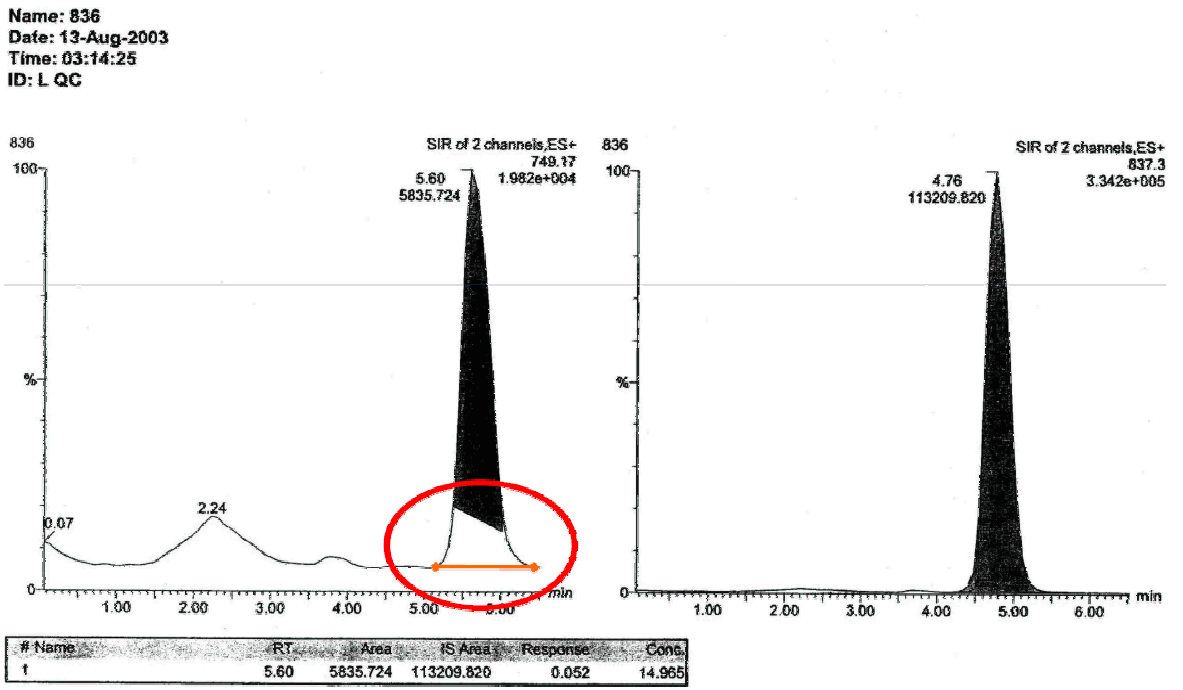
- Questions
  - Study performed and evaluated according to the protocol(s)?
  - Any deviations which might cast doubt on the outcome?
    - If yes, reasonably justified and evaluated accordingly?
    - 'Cherry-picking', *i.e.*, giving the impression that various attempts were made to 'save' an otherwise failing study and report only the best one is not acceptable
      → triggers an inspection
  - Does the study look 'to good' to be true?
    - Compare the results (especially the variability) with information in the public domain (publications, European EPARs, FDA's ANDAs)
      - Studies on different subjects in different clincial settings are not directly comparable but if say, the *CV* is just 25% of the mean of all others
        → consider an inspection

Assessment of BE Studies

- Questions
  - Does the study look ‘to good’ to be true?
    - Examples (mainly from Indian CROs)
      - ECGs identical for all subjects
        → breach of GCP
      - Almost superimpossible concentration/time curves
        → chromatograms simulated, entire study faked
      - Identical peak area of IS in all chromatograms
        → chromatograms simulated, entire study faked
      - Record of IMPs not matching randomization and remaining samples
        → instead of T and R, the reference was administered twice
      - Bioanalytical site unblined
        → samples switched in order pass
      - Audit trail switched off
        → out of control chromatography adjusted and samples reinjected
      - QCs reintegrated
        → make an otherwise failed batch pass

Assessment of BE Studies

- Questions
  - QCs reintegrated
    → make an otherwise failed batch pass
    Inspectors don't like to get fooled *



* LeBlaye O. *Quality issues with bioequivalence trials. Feed-back from French inspections*. Lisbon 2007

Assessment of BE Studies

- Useful Documents
  - Annex VII to procedure for conducting GCP inspections requested by the EMEA: Bioanalytical part, pharmacokinetic and statistical analyses of bioequivalence trials [1]
  - Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples [2]
  - Guidance on triggers for inspections of bioequivalence trials: Quick scan [3]
  - Inspections of Clinical Facilities and Analytical Laboratories Conducting Bioequivalence Studies Submitted in ANDAs [4]
  - Review of Bioequivalence Studies with Clinical Endpoints in ANDAs [5]

1 EMA. GCP Inspectors Working Group. 28 May 2008.
2 EMA. GCP Inspectors Working Group. 28 February 2012.
3 EMA. GCP Inspectors Working Group. 21 February 2017.
4 FDA / CDER. 9 May 2012.
5 FDA / CDER. 26 June 2017.