What does GLP mean in regulated Bioanalysis or Biomarker Bioanalysis

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EBF 9th Open Symposium
16-18 November 2016
Barcelona
Theme of today

“Plasma samples will be analyzed using a validated bioanalytical method”
The science we need to manage

Bioanalysis is the science to accurately and precisely document the concentration of a drug or metabolite in a specific in vivo compartment (plasma, tissue,..) as it was at the time it left the test system (animal, volunteer, patient,…..)

….and a lot can happen on the journey from the needle to the detector
to name just a few…

- Sampling issues (e.g. coagulants, contamination, late or wrong storage,…)
- Stability of analyte (e.g. during sampling, storage or sample preparation)
  - light
  - (bio)chemical - enzymatic
  - F/T, long term, during sample preparation…
- Phys-chem issues (e.g. solubility, adsorption)
- Technology (wrong assay parameters,…)
- Overall documentation issues
- Etc……

→ Why we develop and validate an assay…. 
Developing and validating an assay

Method development (= scientific purposes):
- Preparing the science to allow successful method validation

Method validation (= scientific and regulatory purposes):
- Document the performance of the method prior to its use in production
- Formal testing of the key bioanalytical criteria describing the performance of the method that was developed: accuracy, precision, linearity, sensitivity, specificity, robustness, stability, and some LBA or LC-MS specific parameters…..
- As per FDA, EMA or MHLW Guidance/guideline
Developing and validating an assay
Analyzing study samples

![Graph showing absorption and elimination phases with max and min values]

- Absorption phase
- Elimination phase ($T_{1/2}$)
- $C_{max}$
- $C_{min}$
- $AUC$
- $T_{max}$
But which regulations do we need to comply with for GLP studies?

- When validating an assay:
  - Good question….
  - General understanding in industry = EMA, FDA or MHLW Guidance for Bioanalysis Method Validation (BMV)

- When supporting a GLP study
  - Pretty clear…
  - OECD 1-17 and/or US-FDA 21CFR58
Current thinking in industry

If GLP than BMV
For GLP studies?

Samples must be analyzed using a validated assay as per guidance.

And recently we are starting to add biomarkers into this equations

FDA/CDER-2001 Guidance on BMV

Or

EMA guideline on BMV
Hence

Multiple methods are being developed and validated to support the bioanalysis needs of the GLP study

And because of scope ambiguity….

Additional nonGLP PK studies are preformed to circumvent the GLP challenge for e.g. metabolites, biomarkers or other matrices

Adding to the cost, animal usage or project timelines
But…..Haven’t we mixed up things ?
Regulations and Bioanalysis: Let’s take a deep dive
Which Guidelines regulate our business?

- Guidelines directly related to **Bioanalysis**
- Guidelines related to **our business partners**
- Guidelines **overarching for our industry**

On next 3 slides a rapid overview
Guidelines directly related to Bioanalysis

Full Guidelines
- FDA BMV Guidance, 2001 (US) +
  - industry/FDA ‘consensus’ papers from CC-III, IV
  - Ambiguous: interpretations from 483s, industry/FDA ‘consensus’ paper on CC-V (2013 draft BMV Guidance) – next page
- EMA BMV Guideline, 2011 (EMA)
- ANVISA BMV Guideline 2012 (Brazil)
- MHLW BMV Guidelines 2013 + 2014 (Japan)
- cFDA BMV Guidelines 2015 (China)
- Coming up: ICH M10 (concept adopted June ‘16)

Partial guidelines
- Often related to BA/BE studies, in many countries (HC, TGA,...)
And the ambiguity...

- Publications (2001/2003) authored by industry on LBA - accepted as best practice by FDA
  - not a true ‘Guidance’.
  - Some proposals from these publications are welcomed, accepted (sometimes not fullhartedly), others remain challenged by industry.
- The most challenging ones:
  - Hear-say’ at international BA conferences
  - Observations in Form 483s translated and adopted in industry outside the scope of the 483
Guidelines related to the business partners of BA

- Precinical development: e.g.
  - FDA GLP: 21 cfr 58 (we all saw the new draft.....)
  - OECD GLP: OECD 1(à17)
  - ICH - S3A: Toxicokinetics, microsampling
  - ICH M3 (R2): MIST

- Clinical development: e.g.
  - Bioavailability, bioequivalence
    - FDA: 21 CFR 320.29
    - EMA: CPMP/EWP/QWP/1401/98
  - GCP
    - ICH - E6: Good Clinical Practice : Consolidated Guidance
  - EMA GcLP reflection paper: EMA/INS/GCP/532137/2010
  - Specific BE guidance in almost every country....
Guidelines overarching our industry

- ISO 9000:2000
- FDA guidelines on general principles of process validation
- FDA General Principles of Software Validation; Final Guidance for Industry and FDA Staff
- FDA CFR 21Part 11, Electronic Records; Electronic Signatures — Scope and Application
- Several ICH guidelines related to clinical and preclinical development
- FDA and EMA (draft) guidelines on *in vivo* or *in vitro* testing
- FDA and EMA (draft) guidelines on immunogenicity
- …
From ‘simple’ to ‘reality’

ICH guidelines on preclinical and clinical studies, OECD and FDA guidelines on GLP and/or GCP, safety regulations,…

Built on subjective interpretation: inaccurate translation of Guidelines into SOPs, premature inclusion of ‘hear-say’ at conferences or rumours from 483s in day-to-day processes,…

Adding the non-BA specific Guidelines

Reality in BA

FDA
EMA

MHRA, HC, TGA, ANVISA, literature, meetings, FDA-483,..

Simple thinking
The ‘scope’ question

Scope of BMV Guidance/Guidelines

Scope of GLP for BA
Scope of BMV Guidance?

- Scientific criteria of current guideline/Guidances were largely developed to support clinical BA/BE studies.

- Scope creep has expanded their application to include practically all bioanalytical work, resulting in the inclusion of (scientifically irrelevant and) resource demanding validation assessments on the pre-clinical side and, especially in the early development space, and recently also increasingly for biomarkers.

- Alternative approaches have been developed by industry, to allow better scientific focus and optimize resources spent.
Scope of GLP for BA: FDA

Guidance for Industry, Bioanalytical Method Validation, FDA/CDER, May 2001

“The analytical laboratory conducting pharmacology/toxicology and other preclinical studies for regulatory submissions should adhere to FDA’s Good Laboratory Practices (GLPs) (21 CFR part 58) and to sound principles of quality assurance throughout the testing process. The bioanalytical method for human BA, BE, PK, and drug interaction studies must meet the criteria in 21 CFR 320.29.”
Guideline on bioanalytical method validation, EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2*

Normally, the validation of bioanalytical methods used in non-clinical pharmacotoxicological studies that are carried out in conformity with the provisions related to Good Laboratory Practice should be performed following the Principles of Good Laboratory Practice. ....

Added: OECD Good Laboratory Practice: Frequently asked questions (FAQ)

Unless stipulated in national regulations, there is no requirement to perform method validation in compliance with GLP.

http://www.oecd.org/env/ehs/testing/glp-frequently-asked-questions.htm
But, taking a closer look at GLP Guidelines, which 1-1 references to regulated Bioanalysis can we find?
Are we not over-interpreting GLP for bioanalysis?
What do the GLP guidelines tells us?

Compliance with principles of GLP as stipulated in OECD-1 and 21CFR58 in essence relates to:

- **Resources**: organization, personnel, facilities and equipment.
- **Rules**: protocols, written procedures (SOPs), study director responsibilities and management sign off.
- **Characterization**: test items and test systems.
- **Documentation**: raw data, final report and archives.
- **Oversight** by Quality assurance unit.
And for bioanalysis?

4. Test Methods

Reference to the OECD Test Guideline or other test guideline or method to be used

§ 58.120 Protocol.

(9) The type and frequency of tests, analyses, and measurements to be made.

No requirement to use ‘validated methods as per EMA or FDA guidance’.
A fresh look: building on scientific requirements

Intended endpoint or decisions made

- BA/BE = PK
- GLP = TK
- Biomarkers = a kaleidoscope

Scientific challenges for bioanalysis for GLP?

Similar to BA/BE studies
- Stability
- Reproducibility
- Accuracy & precision (albeit 4-6-20/25 would do fine)

Different to BA/BE studies
- intersubject variability related to matrix
- LLOQ vs ULOQ
- For most studies: Stage of development

Scientific challenges for bioanalysis of biomarkers?

Similar to BA/BE studies
- Stability
- Reproducibility
- Precision (albeit criteria should fit purpose)

to BA/BE studies
- Almost everything else
Hence....

- If compliant with GLP principles, there should be no issue to use alternative validation practices, e.g. validations which covers both the scientific requirements as well as the GLP requirements.

- This gives the opportunity to optimize science, compliance and resources.

Scientific Validation
At the risk of repeating
Tiered approach

Different levels of quality in early discovery assays.
Refer to EBF or GBC paper and relates to research/screening assays

Scientific validation
Refer to 2015 EBF Recommendation paper and relates to 5 assay types where industry tends to use regulatory validation
1. Urine
2. tissue homogenate
3. pre-MAD metabolites
4. non-pivotal ED clinical studies
5. (Non pivotal) Early GLP studies

Regulatory validation
Refer to EMA / FDA / cFDA / MHLW
Should be reserved for pivotal studies that require regulatory action for approval or labeling, such as BE or PK studies

Room for more areas but not specified to date

Fit for purpose = general term, often used in BM assays
A value proposition

Using 25+ years of experience by an expert community committed to deliver quality.

At all times concentration data generated should be in scientific compliance with key bioanalytical quality criteria:

- documented evidence of key bioanalytical parameters
- no cutting corners
- Allow scientific freedom to answer the questions asked
- Documentation should facilitate retrospective review to support other decisions if so required later in development
In practice

**Pre-study validation**

*Predefined criteria*

In practice, if only in-study validation is performed, include (with predefined acceptance criteria) relevant missing parameters from pre-study scientific validation.
EBF recommendation

Tiered approach into practice - scientific validation for chromatography-based assays in early development: a recommendation from the European Bioanalysis Forum.

Bioanalysis, Vol. 7, No. 18, Pages 2387-2398
Tiered approach into practice - scientific validation for chromatography-based assays in early development: a recommendation from the European Bioanalysis Forum.

*Bioanalysis, Vol. 7, No. 18, Pages 2387-2398*

What does this mean for Biomarkers?

- Criteria proposed in recommendation paper were not developed for biomarkers and should not be blindly copied
- Principles however can be applied in sync with the BM paper discussed in previous EBF presentation in this session
1. Observed or anticipated biomarker level changes
2. Development Phase in which a biomarker is measured
3. Decisions taken from the biomarker data
   - efficacy decisions
   - safety decisions
4. Fit of assay with Scientific validation standards
Why do we flag this?

- Cost ↓
- Science ↑
- Focus ↑
- Timelines ↓

- 3R √
Can SV comply with both GLP and scientific requirements?
Bioanalysis =
Requirement on ‘test method’

4. Test Methods
Reference to the OECD Test Guideline or other test guideline or method to be used

§ 58.120 Protocol.
(9) The type and frequency of tests, analyses, and measurements to be made.

For the test method/protocol

Validate as per guidance (regulatory validation)

Apply principles of scientific validation
Does SV fit GLP?

Requirement on test method from OECD 1

4. Test Methods
Reference to the OECD Test Guideline or other test guideline or method to be used.

Requirement on test method from 21CFR58

§ 58.120 Protocol.
(9) The type and frequency of tests, analyses, and measurements to be made.
Bioanalysis = Requirement on ‘test method’

4. Test Methods
Reference to the OECD Test Guideline or other test guideline or method to be used

21CFR 58
§ 58.120 Protocol.
(9) The type and frequency of tests, analyses, and measurements to be made

For the test method/protocol

Validate as per guidance (regulatory validation)

Apply principles of scientific validation
Conclusion

- Common misconception that full compliance with BMV for all studies is necessary
- Compliance with BMV Guidance is not the same as compliance with GLP
- ‘Scientific validation’ can be GLP compliant.
- Scientific rigor and compliance inherent to Scientific validation can save cost, shorten study timelines and support 3R without affecting patient safety
- Can lab data help to convince the broader BA/Stakeholder/HA community on the value of the proposal?

and the same principles are valid for Biomarkers in a GLP study
Refine thinking in industry:

If GLP than an *a priori* defined (scientifically) validated assay yielding valid data is required

a validated assay and BMV are not per default the same
Acknowledgment

EBF community

More info on EBF:
http://www.europeanbioanalysisforum.eu/