Challenges and requirements for reference standards for NBE

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Focus Workshop

(*In collaboration with the AAPS and JBF*)

Industry input into ICH M10: Experimental data as the cornerstone for a science driven bioanalytical guideline

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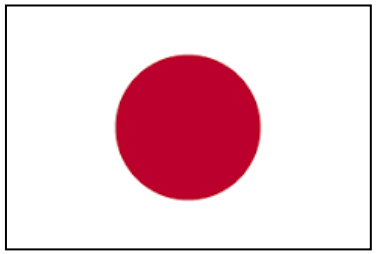
Definition Reference standard

Reference standard is defined as a

- Drug substance
- Drug product
- Well established biologic product that is characterized for use as a calibrator or control



Reference standard:
A compound used as the standard in quantifying an analyte mainly used to prepare calibration standards and QC samples

Challenges and requirements for reference standards for NBE

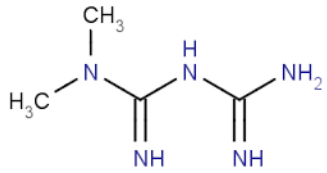
- **Requirements:**

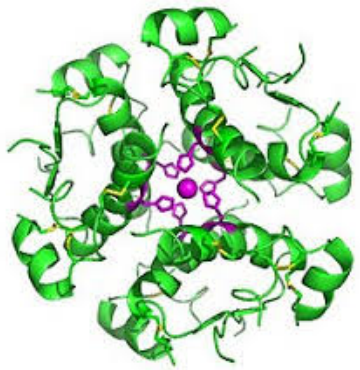
  - Well-characterized
  - should be obtained from an authentic and traceable source (compendia standards, commercially available standards, or in/ex-house produced)
  - CoA required (purity, storage conditions, expiration date and batch number)

Challenges for reference standards for NBE

- During drug development a transition from small to large scale production occurs which can change the Ref Std characteristic and therefore also the affinity to the critical reagents (capture/detection Ab)

- Formulation change can cause unanticipated substances which can bind to the drug

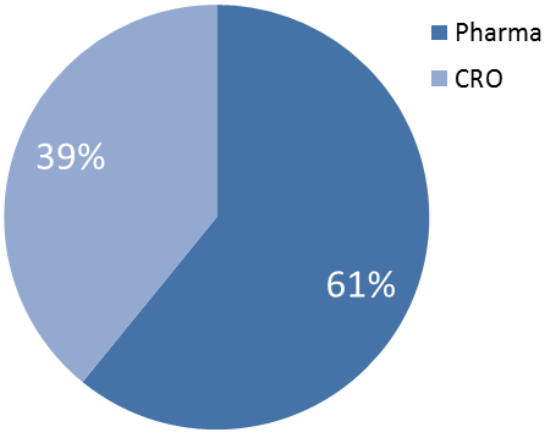




Characteristics	Small molecules	Macromolecules
Size	<1000 Da	>5000 Da
Synthesis	Chemically produced	Biological produced
Structure	Small organic crystalline	Large complex tertiary/quaternary
Purity	Exact / homogenous	Difficult to establish/ heterogeneous
Impurities	Chemically characterized	Difficult to detect, process/host derived
Solubility	Varies	Usually hydrophilic
Instability	Chemical	Chemical, physical and biological

- Survey data

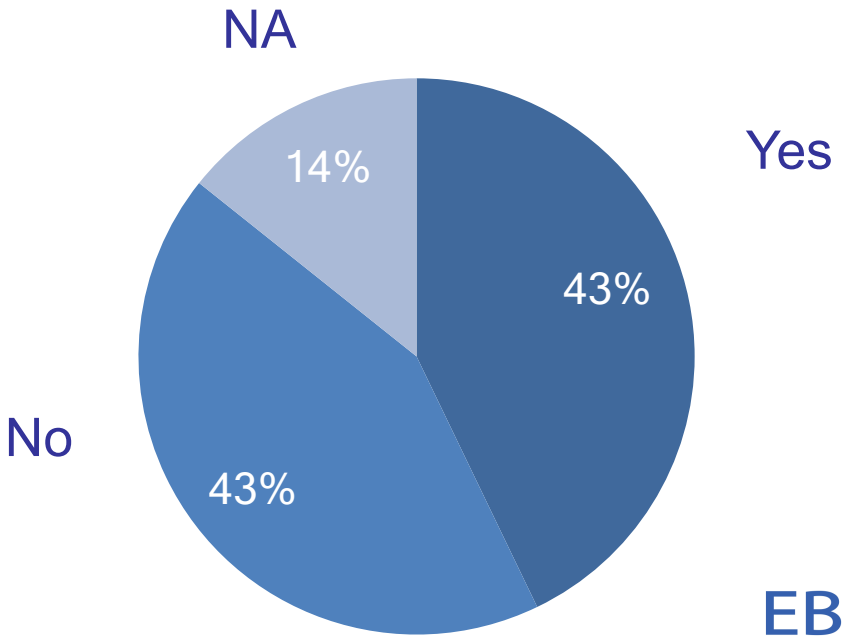
- CRO / Pharma
  - Only Large molecule data



Some white papers state *):

There is a challenge in the development of NBEs as many of the reference standards used for ligand binding assays (LBA) tend to be not well characterized

- Do you agree?



*) GBC paper. Bower et al AAPS J, 2014; 16(2): 352–356

Well-characterized?

What do CMC do for release of reference standard?

- Characterization
  - Content
  - Potency/bioactivity
  - Impurity
  - Homogeneity
  - Relevant quality parameters
  - Stability
  - Compare to reference (USP or non-USP macromolecular reference standard)

USP = United States Pharmacopeia

EBF

EMA guidelines state:

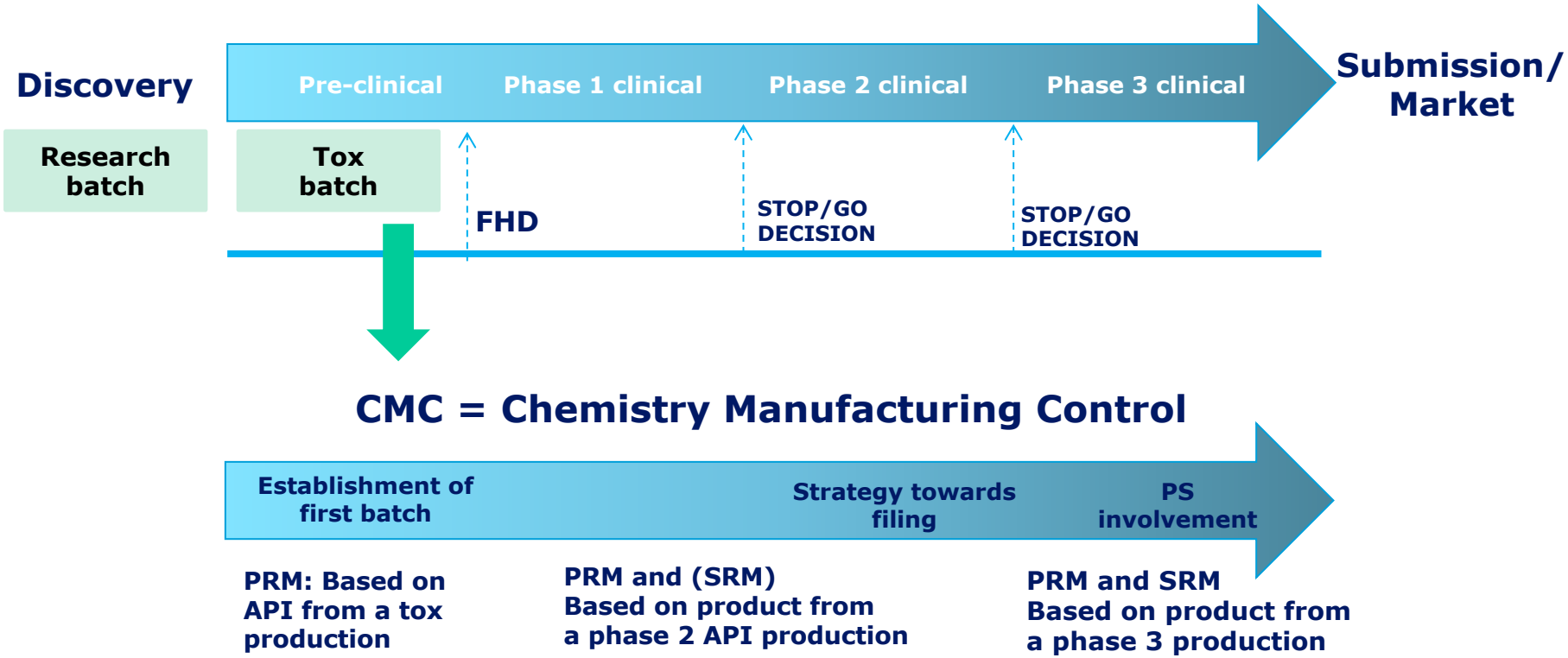
- *The reference material should be well characterised and documented (e.g. certificate of analysis and origin).The purest reference standard available at the time should be procured*.
  - In early development/early GLP tox study, bioanalysis is on the critical path as the GLP-tox batch has just been released.
    Do you use this batch for your assay validation as it is the best characterised?
  - Yes: **94%;** No 6 %
  - Or can you use a batch from Research? Yes 31%, **No 69%**
  - Do you foreseen any difference from the Research batch to the GLP-tox batch ?
    Yes 36% / **No 64%;** Glycosylation issue

EMA guidelines state:

- Do you revalidate your assay when a more pure Ref Std is available?
  Yes 31% / **No 69%**
  - But do perform a bridging-type experiment which include new and old Cal and QCs

What do they do in CMC to release our Reference standard?

- Pharmaceutical development process



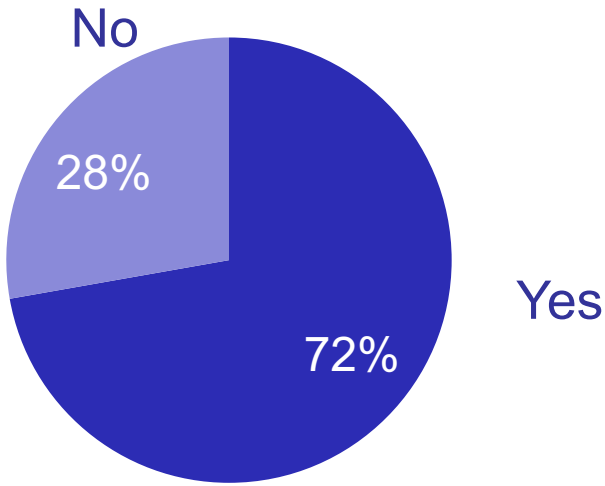
PRM = Primary Reference material, SRM = Secondary Reference material;
API = Active Pharmaceutical Ingredient; PS = Product supply

EMA guidelines

It is strongly recommended that the batch of the reference standard used for the preparation of calibration standards and QC samples is the same as used for dosing in the non-clinical and clinical studies.

– Do you actually do this?

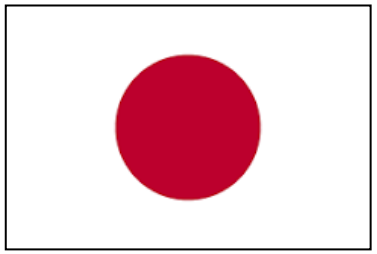
nonclinical & first-in-human studies.



Later clinical studies?

- In phase 3 a Reference Material will be used for Cal& QCs as more than one batch is being used for dosing
- It should not be necessary to use same batch if the batch used is GMP produced
- Not possible to track back which subject was dosed with which batch.
- Only in BE studies

MHLW guidelines



Question & Answers

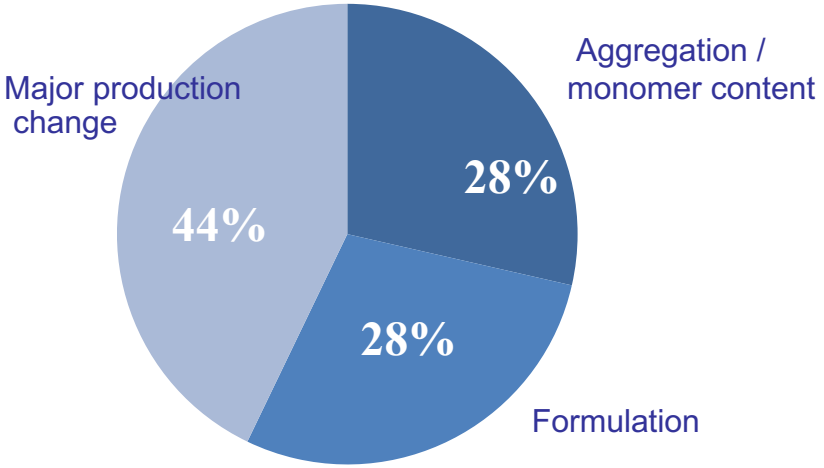
- Q4. Does the reference standard lot have to be the same as the drug substance lot used for dosing in the non-clinical or clinical studies?

- A4. Any lot may be used as the reference standard as long as it conforms to the same quality specifications based on information available from a CoA or other appropriate document. In an early stage of non-clinical studies where a quality specifications for a standard material are yet to be established, it is preferable that the reference standard lot is the same as the drug substance lot used for dosing in the non-clinical studies; if this is not the case, the lot comparability has to be confirmed by an LBA.

EMA guidelines:

In case of change of batch, an analytical characterisation and bioanalytical evaluation should be carried out prior to use to ensure that the performance characteristics of the method are not altered

- Do you perform a bioanalytical evaluation?
  Yes: 62% No: 38%
- And if yes what do you do?
  - 1- 3 Pre&Acc run
  - Bridging experiment
- What do you think constitute a batch change?
- Do not know



- How many times did a change in batch affect your assay
  - Never experienced

Summary = key messages

- A pure, stable & well-characterized reference standard is crucial for a validated PK assay
- Large molecule reference standards are well characterized

Ref Std and dose material:

- If proper comparison of different batch done in GMP environment there should not be a requirement to use same batch of Ref Std for Cal & QC preparation as the dosing batch
  - However, there might be need for this in early non-clinical studies
- Instead of revalidation - perform appropriate bridging experiments of different batch used in a study

Acknowledgement

➢ The EBF community


Thank you


Questions
Answers