NIBR
PKS / BAMSO

Transfer of in-licensed BA Assays for Large Molecule: an uphill Climb to Success

Aleksandra Seydel, PhD
9th EBF YSS Hasselt, Belgium
May-2023

NOVARTIS | Reimagining Medicine

Agenda

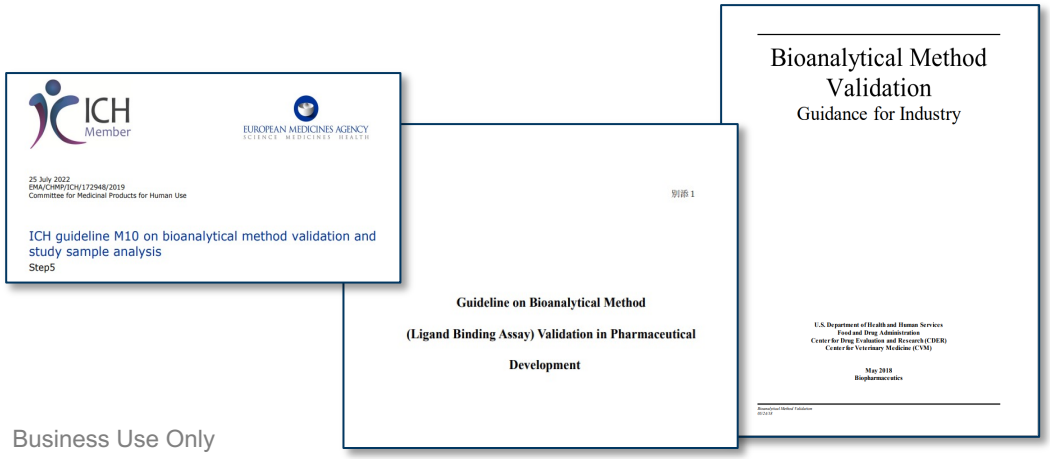
- Increasing demand for BA method transfers
- Regulatory requirements and expectations
- Challenges associated with transfer of BA methods for large molecules
- Case study
- Lessons learned: strategies to mitigate risks related to transfer of BA assays

Demand for BA method transfers

- Drug development programs with complex study designs, incl. several study arms and worldwide locations
  - Increase throughput of sample analysis
  - Country-specific regulations for sample export
- Limited capacities at CROs
- Global redundancy to provide continuity of projects

Regulatory requirements and expectations

- Partial validation to evaluate modifications (transfer) of already validated BA methods
  - One intra-assay A&P determination up to nearly full validation
- Cross validation
  - Comparability and consistency of data generated at different labs



Challenges associated with transfer of BA methods for large molecules

- Demanding scientific character
- Multitude of assays
  - standard Bx PK/PD
  - Three-tiered ADA assay
  - cLBA or cellular NAb (depending on risk assessment)
  - Additional in-study assessments, e.g. cross-validation, selectivity, CP re-evaluation
- Issues to consider in risk assessment:
  - Instrumentation differences
  - Training and analyst experience
  - Critical reagents availability and differences
  - Software differences
  - Minor differences in the method procedure between labs
- Different local requirements (e.g. custom, HA)

Case study - overview

In-licensed compound	• large molecule (mAb) • late phase clinical development
BA assays	• PK, ADA, Nab (cLBA) • established at CRO outside of Europe
Highly accelerated project	• many clinical studies planned • submissions in various indications ongoing or planned • data required within next 6-9 months

Case study – strategy

Transfer of BA methods

Two locations outside of the original CRO's country
Full validation (ADA assays based on signal response)
Cross-validation

BA strategy

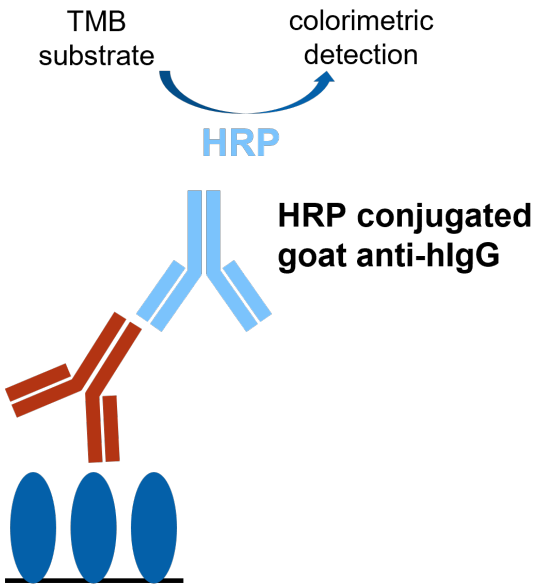
Review of available data and MVRs
Gap analysis (current regulatory requirements)

Critical reagents supply

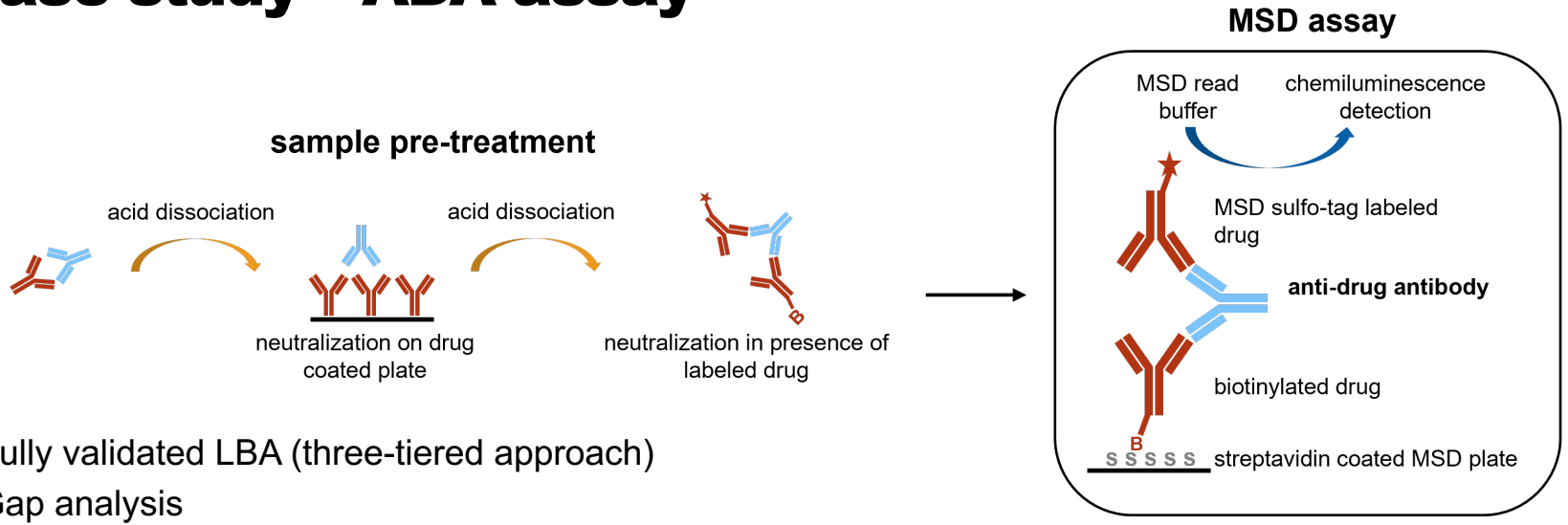
Proprietary reagents
Short-term supply
Long-term strategy

Case study – PK assay

- Fully validated LBA
- Gap analysis:
  - Target interference
  - Interference of co-meds
  - Parallelism with samples at C_{trough}
- Coating reagent (proprietary vs commercial)

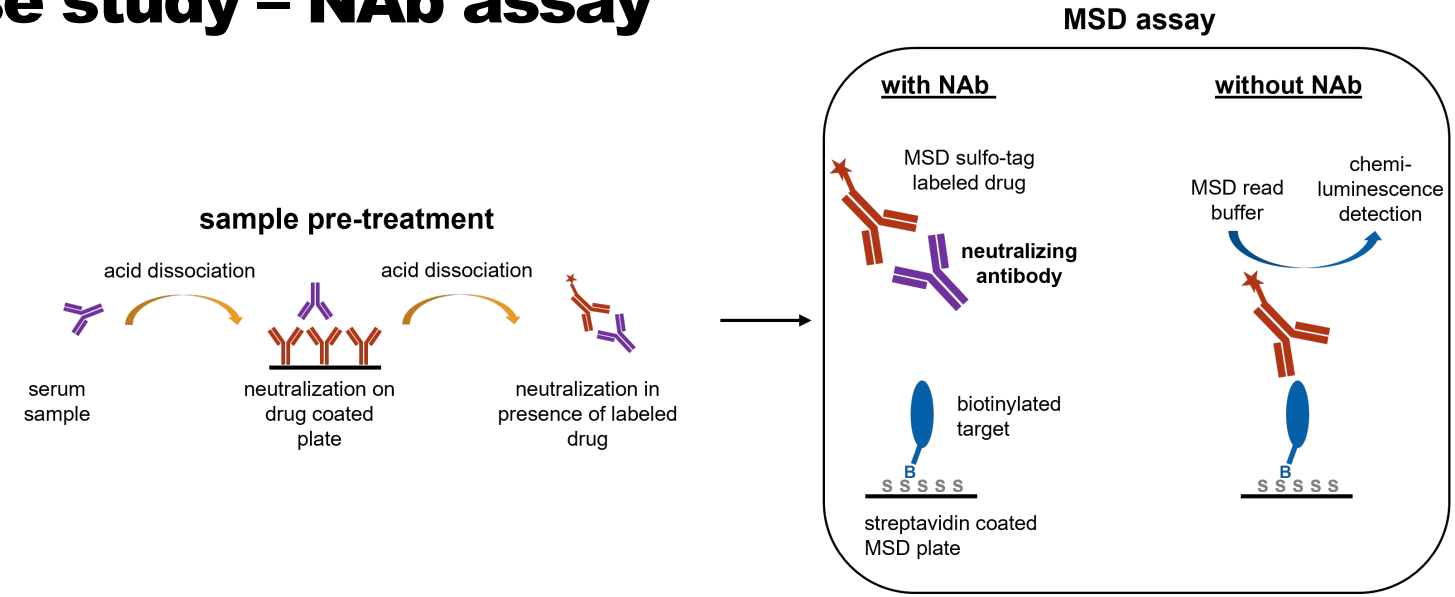


Case study – ADA assay



- Fully validated LBA (three-tiered approach)
- Gap analysis
  - Target interference testing with NC / unspiked serum (risk of false positive results)
  - Interference of co-meds
  - Adjustment of in-study CP for different indications
  - **0.1**% false positive rate was used for calculation of CCPs (vs 1% requested in HA guidance)
- Critical reagents:
  - mPC (proprietary)
  - labeled drug

Case study – NAb assay



- Fully validated cLBA
- Gap analysis
  - Target interference testing with NC / unspiked serum (risk of false positive results)
- Critical reagents:
  - mPC (proprietary)
  - labeled drug

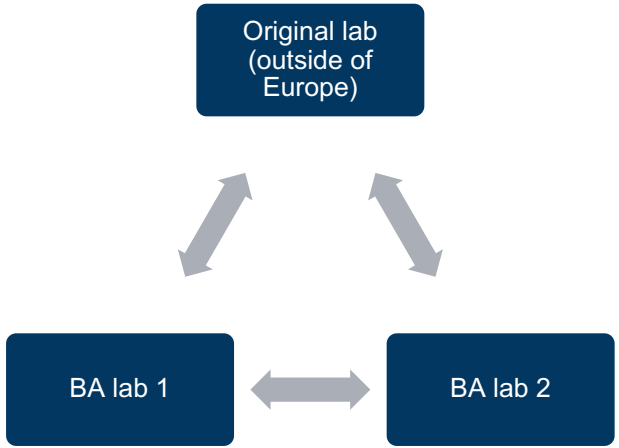
Case study – critical reagents: lessons learned

- Short-term supply & long-term strategy (incl. back-up plan)
- Aliquoting/preparation and thus provided estimates for needed amounts may vary between BA labs
- Various performance of labeled reagents
- The devil is in the detail

Cross-validation

Cross validation is a comparison of validation parameters of two or more bioanalytical methods or techniques that are used to generate data within the same study or across different studies. Also, cross validation is necessary when sample analyses within a single study are conducted at more than one site or more than one laboratory.

- Spiked QCs (n ≥ 30) spanning the range of result outcomes prepared (and analyzed) at reference lab and distributed among others
  - no study samples included due to export regulations
  - > ULOQ?
- QCs analyzed blindly at other labs
- Comparative analysis at the reference lab
- Successful cross validation
  - Acceptance criteria for ADA cross-validation



Case study - outcome

PK, ADA and NAb* assays transferred from one CRO to two other BA labs

Main challenges:

- Revision of BA strategy
- Access to critical reagents supply
- Aggressive timelines for BA deliverables
- *Robust and comparable performance at all three sites

Key(s) to success:

- Intensive monitoring and effective collaboration with CROs
- Comprehensive evaluation of scientific and technical aspects and issues
- Management of expectations

Acknowledgements

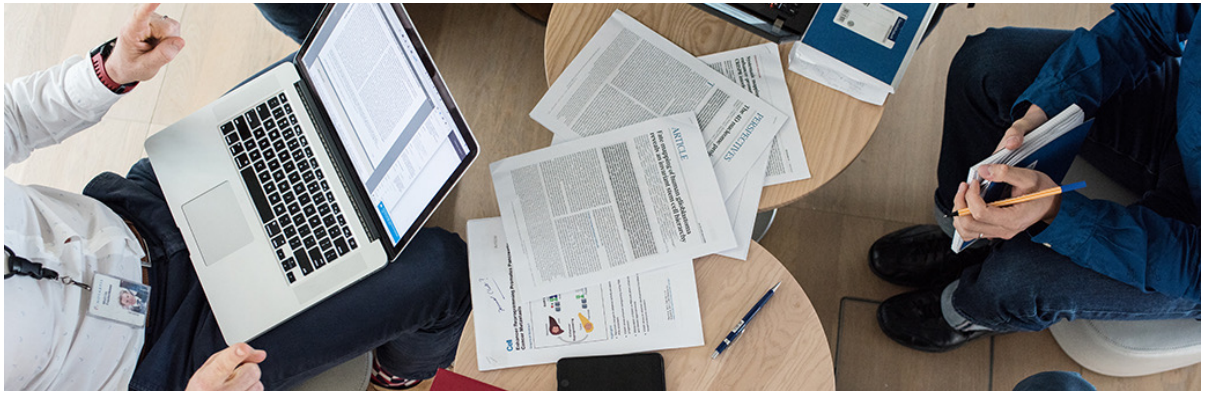
Carsten Krantz
Britta Zehnpfennig
Xianbin Tian
Florent Bender

Discussion

The original cut point was established in one certain population. Assay is being implemented globally, using mixed ethnic group samples.

? How should we look at cross validation assessment?

? How do we define equivalence of methods?



Thank you

NOVARTIS | Reimagining Medicine