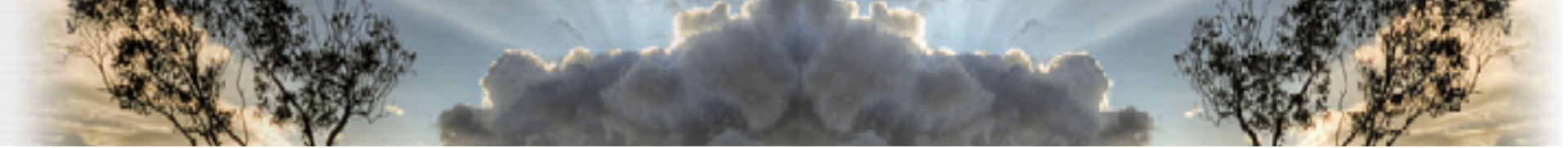


EBF Cyberconnect Events

Focus Workshop: Biomarker Assay Validation and Principles of COU

27th-28th April 2021

The current (assumed) regulatory landscape for biomarker assays

Joanne Goodman, on behalf of the EBF

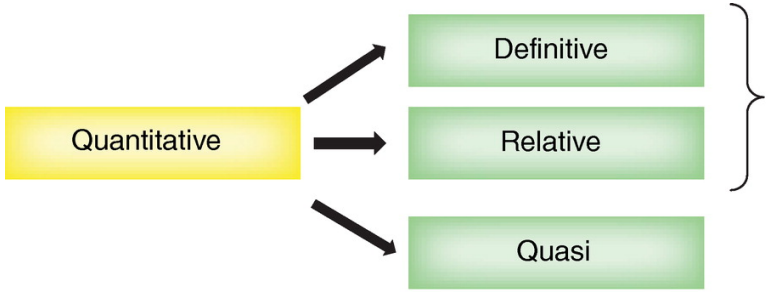
- Background to regulatory BMV guidance
- Biomarkers – is there really a guideline?
- Fear in the regulatory environment
- Be careful what you wish for


A STEP BACK
IN TIME

How did we get here?

- 1990: Analytical methods validation: BA, BE and PK studies meeting of industry and regulators
- Became known as the first Crystal City meeting
- Summarised by Shah (1992)
- First set of expectations for **PK methods** by regulators
- Basis of Bioanalytical Method Validation (BMV) guidance today in multiple regions
- Prior to 2013, Biomarkers for pharmaceutical development never appeared in any guidance document

Biomarker assays are not PK assays



Biomarker levels determined using a reference standard

Reference material is representative of test samples (parallelism)

Reference material not available or not representative of test samples (non-parallelism)

Biomarker levels expressed in terms of a characteristic of the test sample (e.g. assay signal, titre, % bound)

Qualitative

Biomarker levels expressed in nominal (positive or negative) or ordinal terms (e.g. 1 to 5 scoring scale)

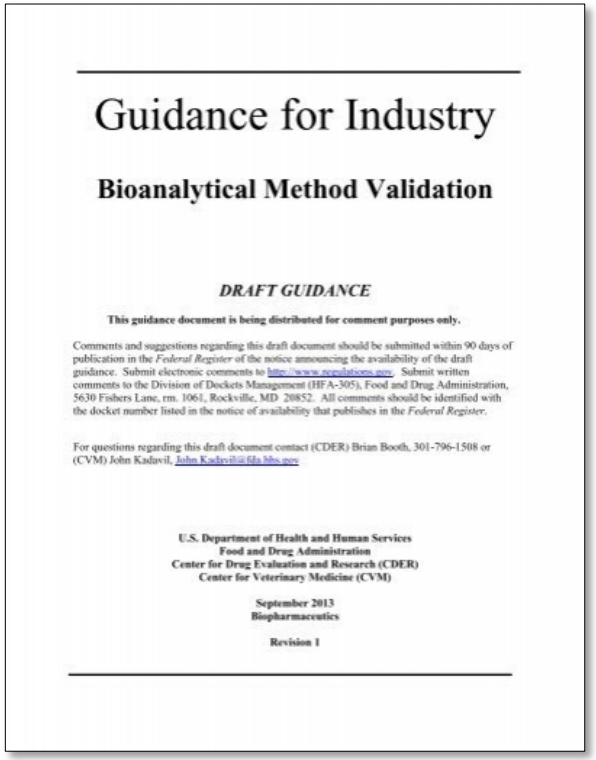
Bioanalysis (2020) 12(20), 1427–1437

COU for biomarkers is not the same as for PK assays
May change depending on data and decisions being made

Diagnostic Biomarkers

- Patient safety, treatment decisions, inclusion/exclusion
- CE/IVD kits
  - Verification that the kit meets the manufacturer's validation
- CLIA regulations for any US laboratory for treatment or diagnosis of a patient
  - Labs outside US can register for CLIA or ISO standard used
- ISO 15189
  - International standard for medical laboratories
- Require an external verification, e.g. CAP, to ensure consistency in testing and processes
- Assay validation is not the same as BMV validation
  - Linearity, range of measurement, LOD/LOQ, precision
  - Accuracy/Trueness is "closeness of agreement with a reference value"
  - Analytical sensitivity and specificity
  - Clinical sensitivity and specificity
- COU could change if a diagnostic is used for a different purpose

Things started to look different …..



Guidance for Industry

Bioanalytical Method Validation

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Brian Booth, 301-796-1508 or (CVM) John Kadavil, John.Kadavil@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)

September 2013
Biopharmaceutics

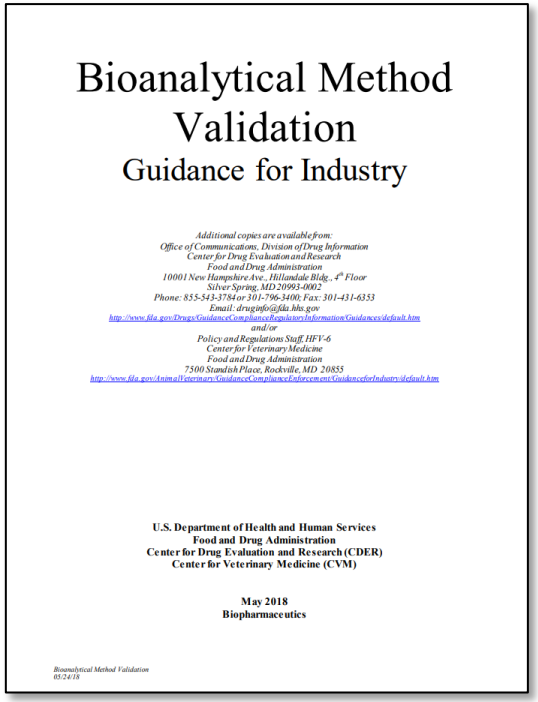
Revision 1

Selective, sensitive, and validated analytical methods for the quantitative evaluation of drugs and their metabolites (analytes) and biomarkers are critical for the successful conduct of nonclinical and/or biopharmaceutics and clinical pharmacology studies. Validating bioanalytical methods includes performing all of the procedures that demonstrate that a particular method used for quantitative measurement of analytes in a given biological matrix (e.g., blood, plasma, serum, or urine) is reliable and reproducible for the intended use. Fundamental parameters for this validation include the following:

- Accuracy
- Precision
- Selectivity
- Sensitivity
- Reproducibility
- Stability

Reaction from industry

Did we understand the final FDA guidance?



Bioanalytical Method Validation

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
and/or
Policy and Regulations Staff, HFV-6
Center for Veterinary Medicine
Food and Drug Administration
7500 Standish Place, Rockville, MD 20855
http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)

May 2018
Biopharmaceutics

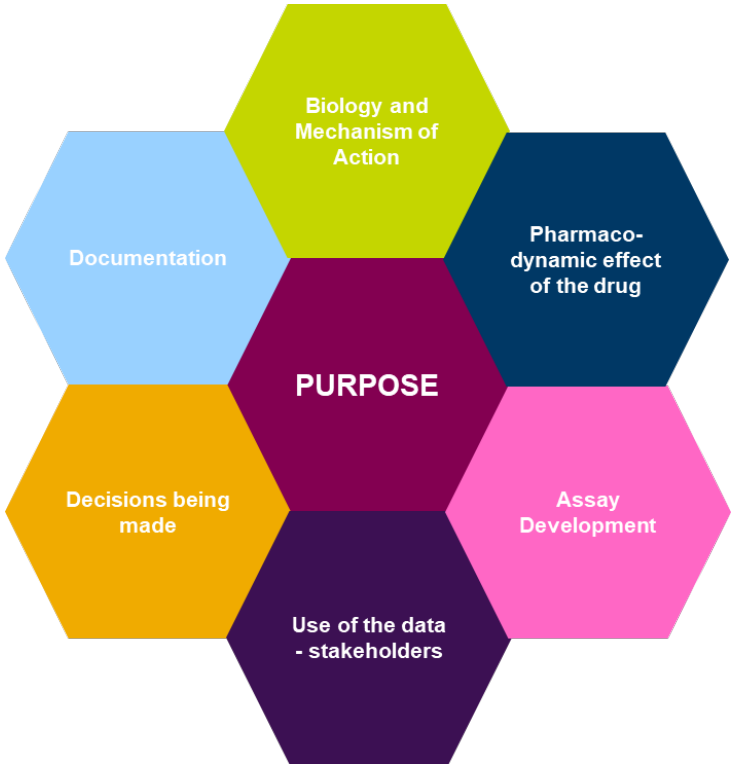
Bioanalytical Method Validation
05/24/18

The information in this guidance applies to bioanalytical procedures such as chromatographic assays (CCs) and ligand binding assays (LBAs) that quantitatively determine the levels of drugs, their metabolites, therapeutic proteins, and biomarkers in biological matrices such as blood, serum, plasma, urine, and tissue such as skin.

- Brings the focus on the assay validation
- But maybe we were not good at reading …..
- "Quantitatively determine"
  - Of the many biomarker assays the bioanalytical scientist develops / implements, few fall into this category

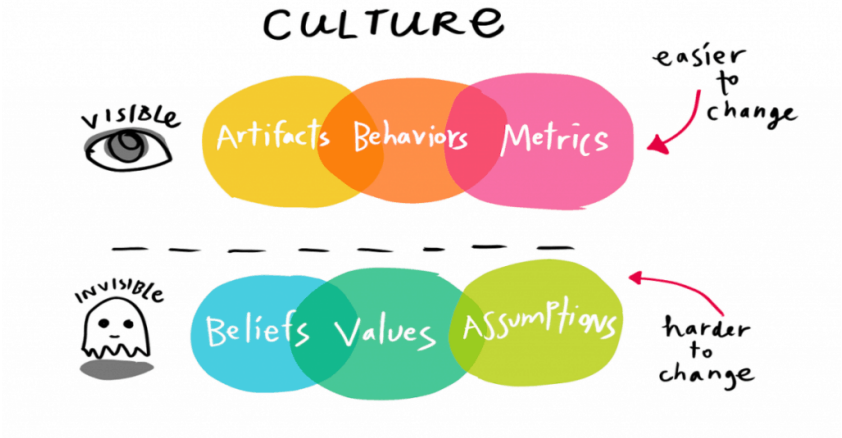
COU is the all about “Purpose”

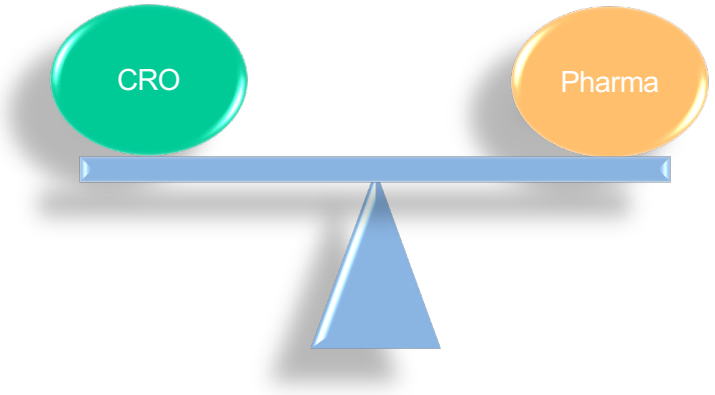
- “The fit-for-purpose (FFP) concept states that the level of the validation should be appropriate for the **intended purpose of the study**.” FDA Guideline 2018
- “**Pivotal studies** submitted in an NDA, BLA, or ANDA that **require regulatory decision making for approval, safety or labeling**, such as BE or pharmacokinetic studies, should include bioanalytical methods that are fully validated.” FDA Guideline 2018
- Risk that both industry and regulators do not interpret and apply the guidance in the same way



The problem statement: the desire for regulations to make us feel comfortable

Added dimensions that may confound the situation

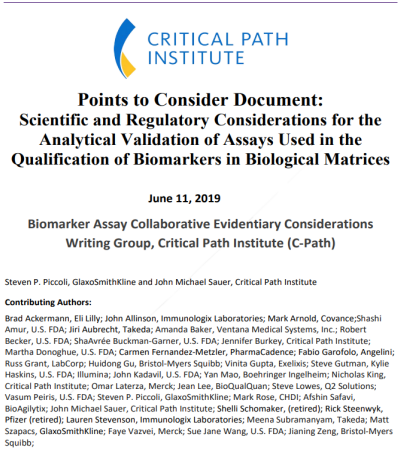




- Regulatory questions may be viewed negatively within some organisations
- Fear rather than opportunity for discussion
- Organisational structure may hinder COU conversations and understanding
- PK SOP exists and serves as an easy option
- Pharma may not supply CROs with enough information around COU
- CROs may not ask for all the information
- Fear of 483s and business ramifications

So do we need guidance?

- Regulatory guidance cannot cover all eventualities for biomarkers within pharmaceutical development
- Existence of white papers for things to consider
- Regulation will only serve to remove the act of thinking and create “tick box” mentality
- What is needed is scientific and “**biomarker thinking**”
- Following guidance doesn’t automatically make an assay the right assay for the intended purpose to get the right data



CRITICAL PATH INSTITUTE

Points to Consider Document: Scientific and Regulatory Considerations for the Analytical Validation of Assays Used in the Qualification of Biomarkers in Biological Matrices

June 11, 2019

Biomarker Assay Collaborative Evidentiary Considerations Writing Group, Critical Path Institute (C-Path)

Steven P. Piccoli, GlaxoSmithKline and John Michael Sauer, Critical Path Institute

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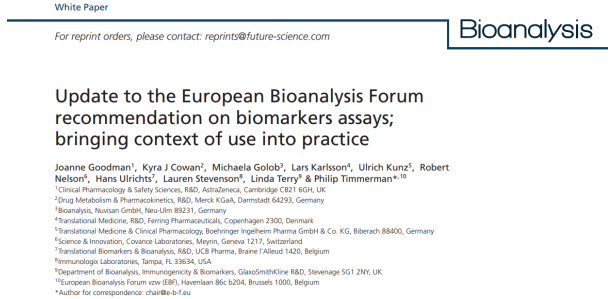

White Paper

For reprint orders, please contact: reprints@future-science.com

Bioanalysis

Update to the European Bioanalysis Forum recommendation on biomarkers assays; bringing context of use into practice

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Challenge your mindset

- Patients are waiting
- We owe it to them to put science first
  - Right biomarker assay
  - Appropriately validated for the intended purpose
  - Right data
  - Right decision
  - Right population
- PK guidance is not the right approach
  - Risks the wrong data and the wrong decision(s)
- Need to change the paradigm what defines a guidance
- We need to address the “fear” and give the community tools

Acknowledgements

- Training Day team
- EBF SC

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European Bioanalysis Forum vzw

www.e-b-f.eu