

NUVISAN

PK as a context of use:
putting science back in
prime time

Dr. Fabian Gärtner

Team Lead PK/TK evaluation and Data management BioA

18th EBF Open Symposium

**THE
SCIENCE
CRO**

„Context of use“ - more than a biomarker phrase

Well established, common phrase when talking about biomarker

Context of use is a strategic enabler – it transforms validations from a technical task into a decision driven process

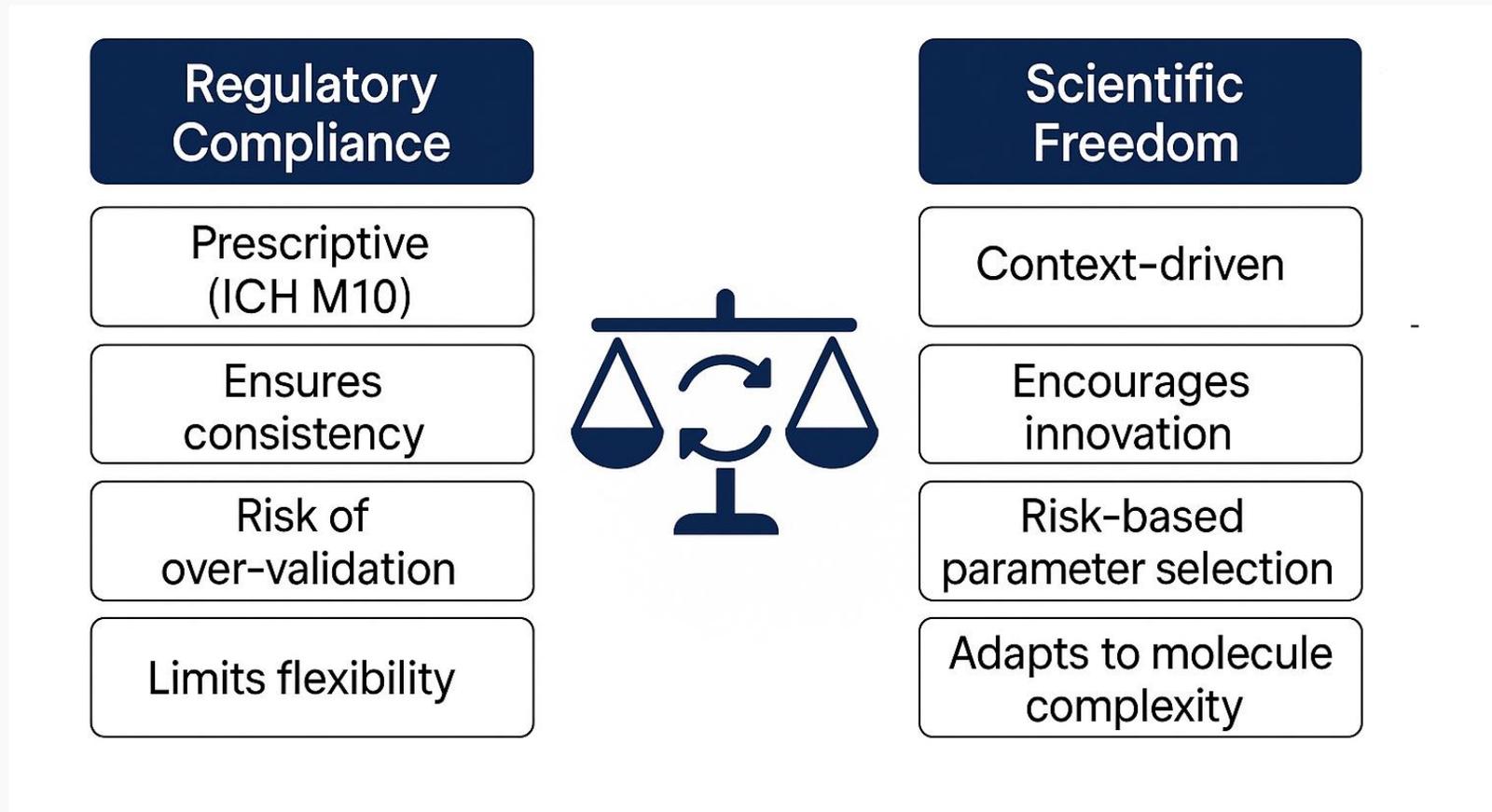
- overall design of the assay
- underlines the definition of acceptance criteria
- the Lower Limit of Quantification (LLOQ)

Diverse and individual validation program, tailored specifically to each biomarker's unique characteristics and intended application

→ Resource effective validation program that answers all open questions to generate meaningful data for all stakeholders

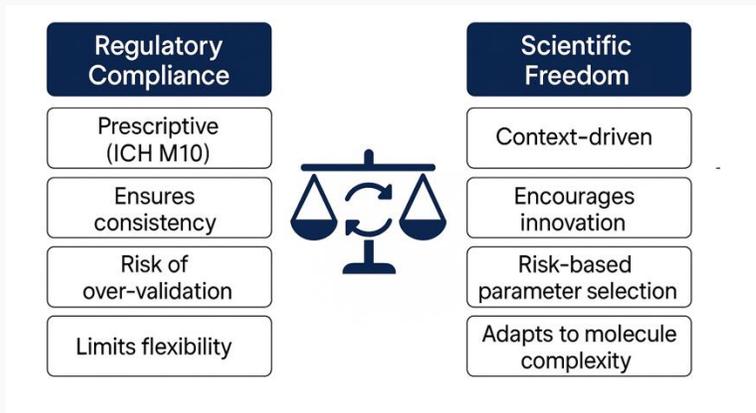
PK Validation: Balancing Scientific Freedom and Regulatory Compliance

While biomarker validation embraces flexibility, PK validation often defaults to rigidity - how can we bridge this gap?



PK Validation: Balancing Scientific Freedom and Regulatory Compliance

While biomarker validation embraces flexibility, PK validation often defaults to rigidity - how can we bridge this gap?



“Changes from the recommendations in this guideline may be acceptable if appropriate scientific justification is provided.” *ICH M10, Chapter 1, 1.1*

- **Challenge:** PK validation can become a checklist exercise
- **Opportunity:** Apply context-driven flexibility without compromising compliance

Not all studies require full ICHM10 validation → context defines the depth!

Some studies require to go further than what ICH M10 is requesting

PK: more than just one assay

- PK assay does not equal PK assay

Assay Type	Purpose	Importance	Strategic Relevance
Free PK	Measure unbound drug	Reflects pharmacologically active fraction	Critical for dose optimization and PK/PD modeling
Total PK	Measure bound + unbound drug	Complete exposure profile	Supports safety assessment and regulatory submissions
Bi-Active PK	Measure active forms/metabolites	Evaluates efficacy and toxicity	Essential for complex biologics and personalized dosing

- Assay choice impacts clinical decisions, regulatory strategy, and resource allocation

Passing PK assay information along

Thinking outside the silo is very important, since the difference between free / total / bi-active ... data can highly influence the model built by PK scientists

➤ **Dose Optimization:**

- **Free Drug:** Critical for determining the effective dose, as it directly correlates with the drug's therapeutic effects. PK scientists need to ensure that the dosing regimen maintains adequate free drug levels
- **Total Drug:** Important for safety and toxicity considerations, as total drug levels can indicate potential accumulation and risk of adverse effects

➤ **Pharmacologically Active Drug:**

- **Free Drug:** Only the unbound (free) drug is pharmacologically active and able to interact with its target. Knowing the free drug concentration helps in understanding the drug's therapeutic efficacy and mechanism of action
- **Total Drug:** Includes both bound and unbound drug. While it provides a complete picture of drug presence, it doesn't directly indicate the amount available for pharmacological activity

➤ **PK/PD Correlation:**

- **Free Drug:** Directly correlates with pharmacodynamic (PD) effects, helping to establish a more accurate PK/PD relationship
- **Total Drug:** Offers a general correlation but may not precisely reflect the PD effects if the drug is extensively bound to proteins

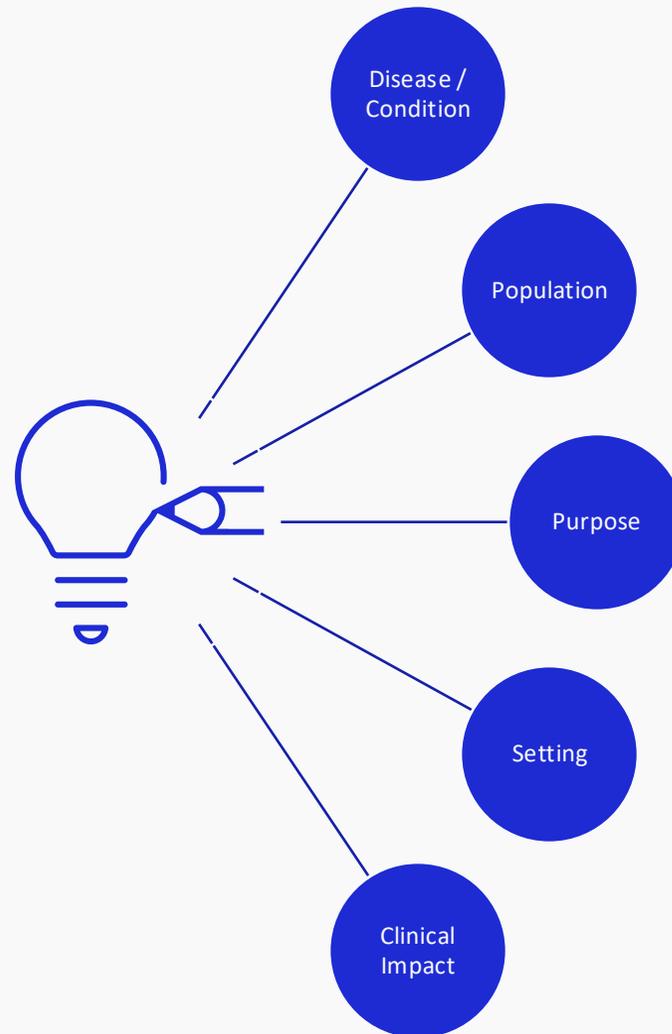
PK: more than just one assay

- PK assay does not equal PK assay

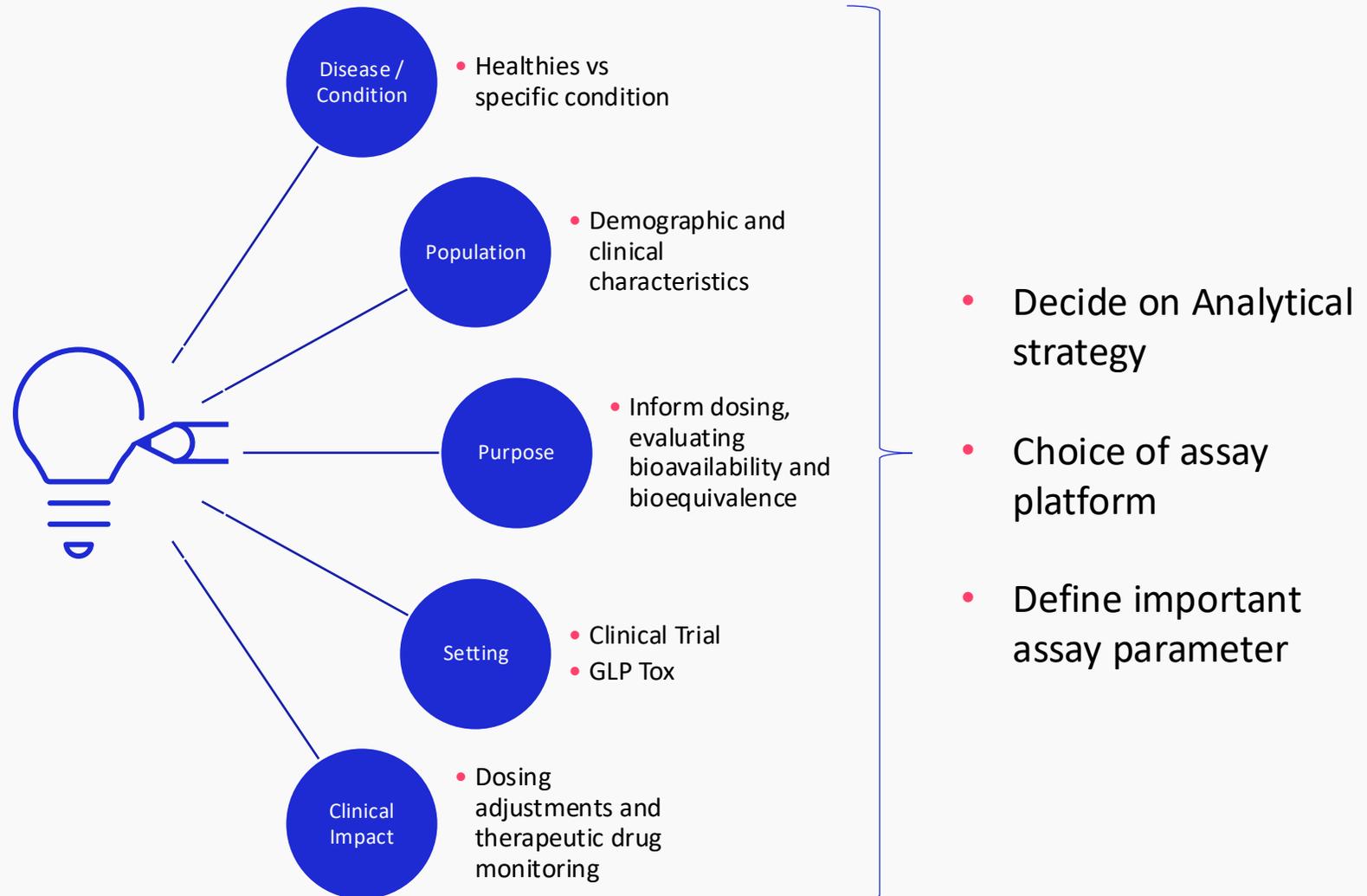
Assay Type	Purpose	Importance	Strategic Relevance
Metabolite PK Assay	Measure active or toxic metabolites	Completes PK profile; critical for understanding efficacy and safety	Essential for small molecules, supports dose adjustments and risk mitigation
Secondary Matrix PK	Assess drug/metabolite in urine, CSF, tissue	Provides clearance and excretion data; supports special population studies	Required for mass balance studies, mechanistic understanding

- Assay choice impacts clinical decisions, regulatory strategy, and resource allocation

Key aspects of context of use for bioanalytical assays



Key aspects of context of use for bioanalytical assays



From Context of Use to Validation Strategy

PK combined context of use statements

- Drug 1/2/3 is being investigated for treating disease Y. Free / Total / Active (free) drug levels shall be analyzed for this bi-specific antibody in serum from healthy volunteers and in patients suffering from disease Y. It is expected that drug levels increase to a Cmax of XXX and will decrease in a linear fashion. The assay shall be selective, robust, accurate and precise, since the data is needed to support dose selection and therapeutic drug monitoring / and generation of safety data (exposure). The samples will be analyzed in batches and meanwhile stored at -75°C.
- Due to conserved parts, it is possible start with the guideline with standardized and stringent framework that defines the validation parameters

Accuracy and Precision

Selectivity in healthy individuals and patients suffering from disease Y

Stability with a level at least covering Cmax

Dilution linearity diluting a Cmax level into the dynamic range

From Context of Use to Validation Strategy

PK combined context of use statements

- Drug 1/2/3 is being investigated for treating disease Y. Free / Total / Active (free) drug levels shall be analyzed for this bi-specific antibody in serum from healthy volunteers and in patients suffering from disease Y. It is expected that drug levels increase to a Cmax of XXX and will decrease in a linear fashion. The assay shall be selective, robust, accurate and precise, since the data is needed to support dose selection and therapeutic drug monitoring / and generation of safety data (exposure). The samples will be analyzed in batches and meanwhile stored at -75°C.
- Scientific thinking must still drive parameter selection beyond the required parameter

Parameter outside of the ICH M10:

Target interference

Specific requirements towards dilution linearity

From Context of Use to Validation Strategy

Risk-based approach avoids unnecessary testing while maintaining compliance



- Avoid over-validation → saves time/resources
- Focus on parameters that matter for decision-making
- Aligns with ICH M10 flexibility

Summary of Validation Parameters: Driving Scientific Leadership

Scientific ownership of validation strategy ensures relevance, efficiency, and regulatory robustness

Mandatory (ICH M10)	Context-Driven
Accuracy	Parallelism
Precision	Target interference
Stability	Extend of stability assessment
Dilution linearity	Extent of dilution linearity
Selectivity	(ISR)

Avoids over-validation and adds scientific insight where needed

Excessive validation wastes resources, delays projects, and reduces the scientific relevance of results

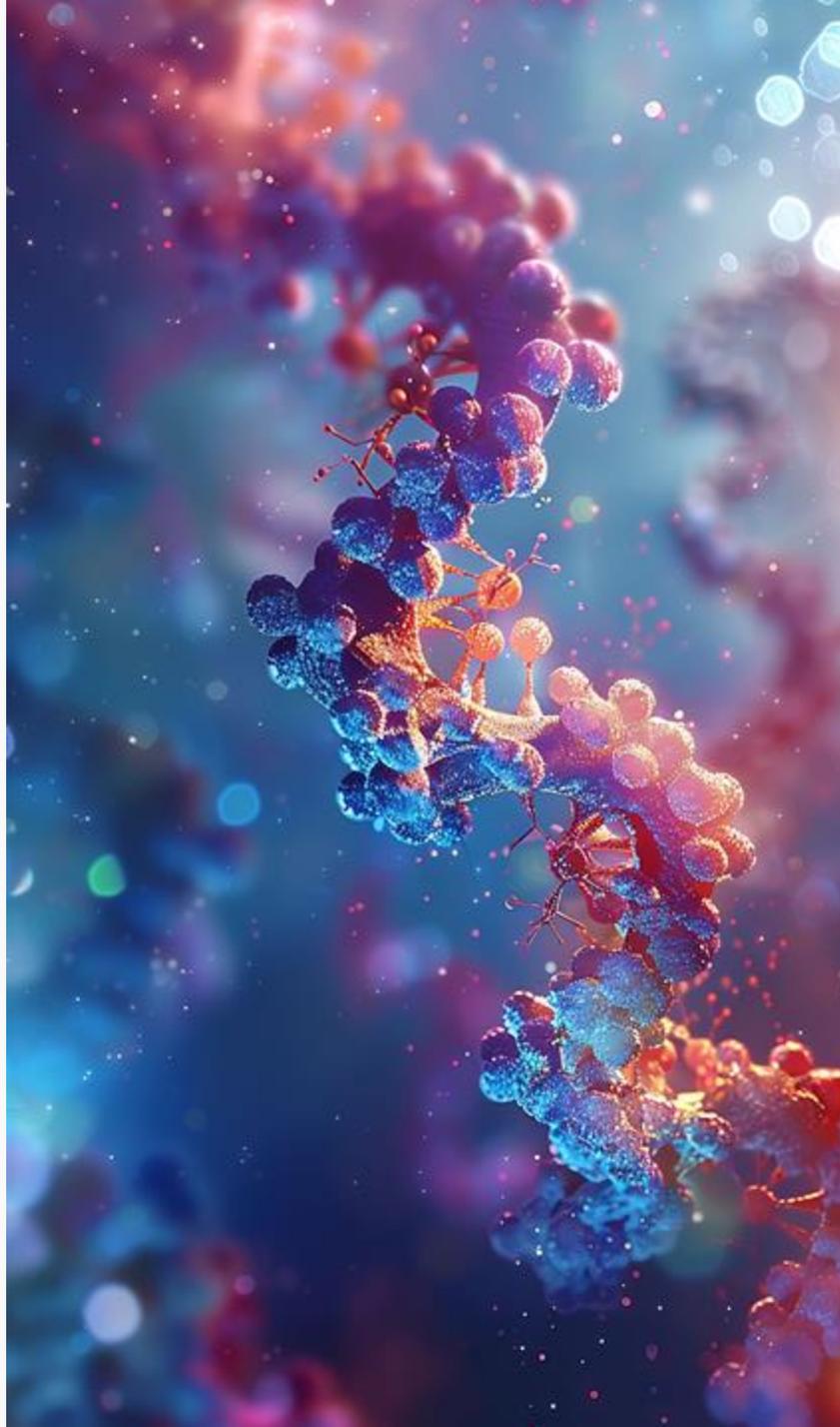
Context defines which parameters are critical - not the checklist.

Context-of-use should not just be used as a statement — it is the foundation for **scientifically justified, efficient and regulatory-compliant** validation.

- **Move beyond checklists:**
Avoid rigid application of ICH M10; embrace flexibility whenever justified.
- **Focus on efficiency:**
Strategic validation avoids over-validation, while saving time and resources.
- **Enable cross-functional impact:**
Clear context-of-use improves PK modelling, and therefore dose optimisation, as well as regulatory confidence.

**THANK YOU FOR YOUR
ATTENTION!**

Any questions?



Acknowledgments

Michaela Golob
Katja Zeiser