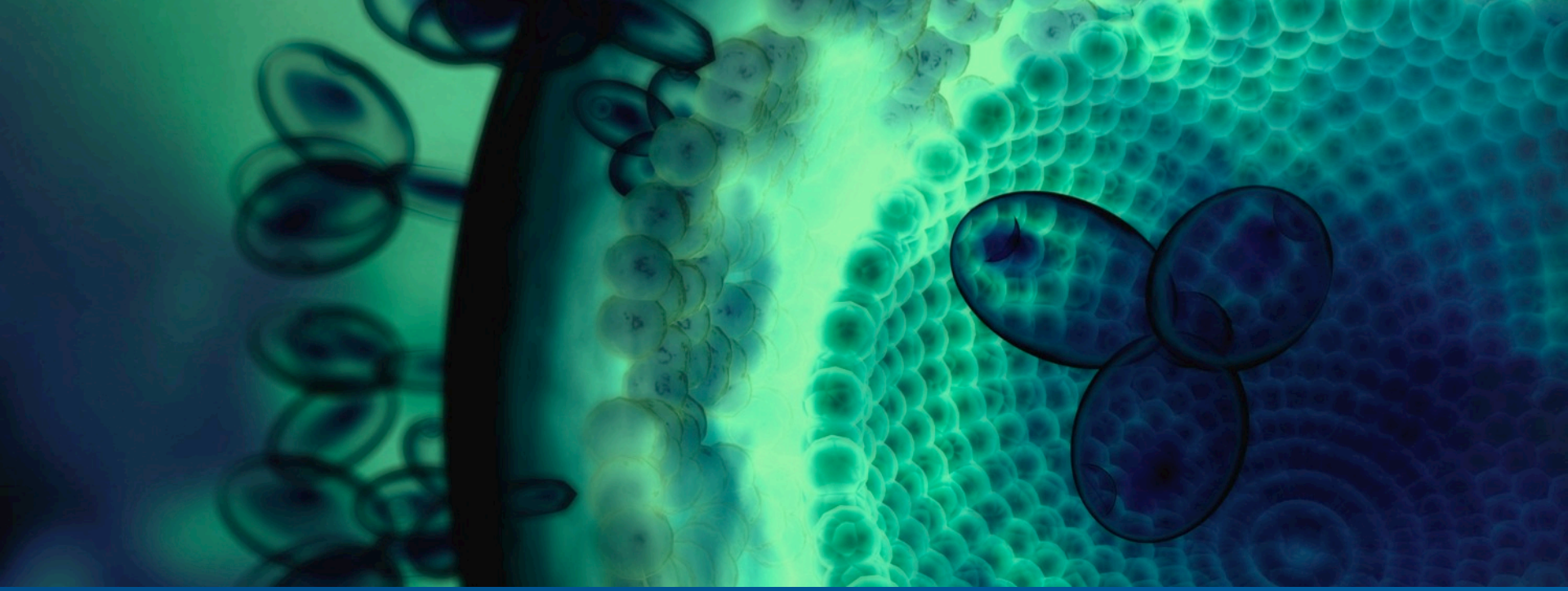

Tiered Approach for Bioanalysis of Drugs and their Metabolites

Pictured above: The structure of HIV.

Examples of the Use of Qualified Assays at Janssen R&D during the past decade

Hans Stieltjes| EBF 7th Open Symposium Barcelona| 19 Nov 2014

janssen | PHARMACEUTICAL COMPANIES OF Johnson&Johnson

Overview

- Introduction
- Tiered Approach Strategy
- When do we typically use regulated or scientific validations?
- Some recent examples of where we used qualified assays/ scientific validation
- Response from and to regulators
- Conclusion

Introduction

Qualified assay (Tiered Approach, **Scientific validation**) vs regulatory validation

Right balance between:

- Appropriate level of scientific validation (assay, stage)
- Need of regulatory method validation
- Extent of supporting method development

Within a study, the choice may differ between the drug and its metabolites, and also between various matrices of interest.

Ref: EBF presentation by Philip Timmerman/Steve White: Taking tiered approach to the next level: Feedback from the workshop

Tiered Approach Strategy

Discovery

Sc. Validation

No pre-validation
Minimal batch acceptance
Stage appropriate science

Examples:

- Early PK
- In-vitro
- Early Safety

Development

Sc. Validation

Stage appropriate MD
Pre-validation
SOP driven
Limited report

Examples:

Reg. Validation

Extensive MD
As per guidelines

Examples:

Next Slide

When do we typically use regulated or scientific validations?

Study type	Matrix	Analyte	Regulatory Validation
Clinical			
	Plasma	Parent	After MAD
		Metabolite	Beyond Phase 2
	Other: urine, CSF	Parent, Metabolite	
GLP TOX	Plasma	Parent	✓
		Metabolite	If toxicity flag
	Other: tissues	Metabolite	
non-GLP PK/TK	Plasma, tissue…	Parent, metabolite	
in vitro	Plasma, blood, buffers, …	Parent, metabolite	

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		Metabolite	If toxicity flag	✓
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non-GLP PK/TK	Plasma, tissue…	Parent, metabolite		✓
in vitro	Plasma, blood, buffers, …	Parent, metabolite		✓

Some recent examples of where we used qualified assays/scientific validation

Case:

1. Metabolite analysis in non-clinical studies

2. Urine analysis of parent compound and metabolites at CRO

3. DDI study at CRO: Analysis of metabolites from concomitant drug in plasma and urine samples

Case 1
Metabolite in non-clinical studies

FEATURES	
Stage of Development	Phase I
Scientific points of attention	See next slide
Pre-validation	NO
Reporting	Results only
Filing	IND

Case 1
Metabolite in non-clinical studies

- Metabolite already measured with validated assay (combi-assay with parent) in early GLP TOX studies before in-licensing
- Not active, abundance only a few percent, no clear TOX indication
- Metabolite analysis not required in this stage, but to bridge results with earlier studies applied anyway, using a scientifically validated assay

- However, due to in-vitro potential for gen-tox related to the metabolite, a regulatory validated assay for use in carcinogenicity study in the mouse was applied

Case 1
Metabolite in non-clinical studies

Method development

- Conversion parent into metabolite (factor 10 higher parent concentration)

- Instable secondary phase 2 metabolite(s)

Filing

- IND : "The method for COMPOUND was validated and used for the later GLP toxicology studies (...) For the 6-month transgenic mouse study, bioanalysis methods for COMPOUND and for the METAB in plasma were validated. For the other species, METAB was determined using qualified assays."

Case 2
Urine analysis of parent compound and metabolites at CRO

FEATURES	
Stage of Development	Phase III
Scientific points of attention	See next slide
Pre-validation	NO
Reporting	full report
Filing	NDA

Case 2
Urine analysis of parent compound and metabolites

Method development

- Evaluation of adsorption and short-term stability in urine at various pH, testing with and without additives

- Test the method as used for plasma samples regarding selectivity and assay performance

- Test potential conversion of metabolites to parent

Case 2
Urine analysis of parent compound and metabolites

Filing

In CTD:

- "Qualified methods, i.e., scientifically sound methods with documented preset acceptance criteria were used for analysis of ANALYTES in urine samples"
- "The samples were analyzed using the plasma assay as described in 'MV STUDY' but adapted to urine as matrix"
- No method details or performance evaluations
- Reference to analysis reports

Comments from FDA and EMA

- None

Case 3
DDI study at CRO: Analysis of metabolites from concomitant drug in plasma and urine samples

FEATURES	
Stage of Development	On market
Scientific points of attention	See next slide
Pre-validation	YES, but…
Reporting	full report
Filing	sNDA planned

Case 3
DDI study at CRO: Analysis of metabolites from concomitant drug in plasma and urine samples

Method development

- Literature search for expected levels and potential impact of co-administration

- Test suitability of sampling conditions (plasma/urine; adsorption, stability)

Pre-validation

- Prepare long-term stability samples
- Wait with pre-validation/analysis on go/no-go decision from team

Case Conclusions

Advantages of the Scientific Validation Approach

- Flexibility to adapt range or method
- Changes are without consequences for reporting timelines
- Resource/Cost saving

Focus on **relevant** science

Summary of regulatory feedback

Since 2003 Janssen submitted files for 13 NMEs to the regulators in different parts of the world. These files also contained data generated by qualified assays (scientific validations)

- Only limited number of questions
- Essentially, Health Authorities seeked explanation of what a qualified assay consisted of

..and here is how we responded

- For the determination of analyte concentrations in urine samples, a qualified method was set up. This is a method with an appropriate level of scientific validation (e.g., accuracy, precision, stability). When applied to study samples, the qualified method generates absolute concentration data which allow documented and reproducible decision making. In addition, the method establishment for the qualified urine assay focused on sampling and storage of the urine samples.
- For the determination of the analyte in urine, a method was set up under method development and a qualified analytical method (QAM) was written before the start of the analyses. No prestudy validation report was written. Quality control samples were used for the acceptance of the analytical runs of the study samples.

No further questions received and drugs were approved!

Conclusion

- At Janssen, Scientific Validations (Qualified Assays) have been used for a number of years already.

- The type of study, matrix and the stage in development drive
  - Decision to go for scientifically or regulatory validated assay.
  - Level of scientific validation, and required method development
  - Level of documentation and reporting

- Drivers are: flexibility, resources and appropriate science

- Health Authorities do accept data from so-called 'non-validated' assays, but not all are (yet) familiar with the concept

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