Challenges and Learnings from Validation of AAV Neutralizing Antibody (NAb) Assays under IVDR

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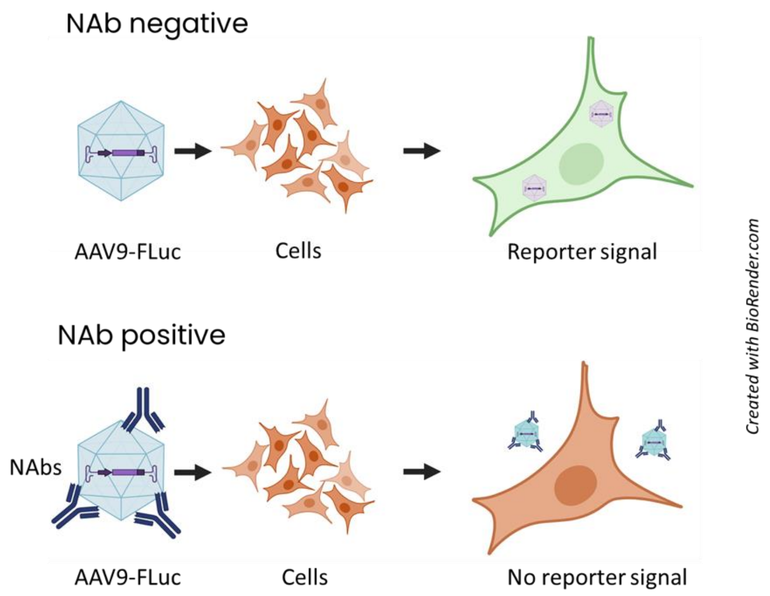
Introduction

- Compound type: AAV-based Gene Therapy
- Viral vectors effectively interact with human cells, deliver their genetic material, and express their proteins.
- Previous exposure to virus may compromise safety and/or efficacy of the therapy.
- Antibody titers have been assigned as inclusion or exclusion criteria for gene transfer therapy protocols.

Cell-based Neutralizing Antibody Assay (Nab) against AAVx capsid



Introduction

Scope	1) **Screen patients for neutralizing antibodies for inclusion/exclusion purposes → IVDR** 2) Assess neutralizing activity as clinical endpoint → **GCP/IVDR**

- Assay first validated according to GCP requirements in the USA
- Assay was later validated to fulfill IDE requirements in the USA

→ Best approach for both GCP and IVDR compliance in Europe?

Approach: Hybrid validation

Regulatory Requirements for IVDR (In-house test approach)

- GCP compliance
- Single health institution
- ISO 15189 compliant processes or certification
- Compliance with IVDR Annex I General Safety and Performance Requirements (GDPR), e.g. by setting up a Technical Documentation according to Annex II of IVDR

Approach: Hybrid validation

Assay Requirements

- Ability to detect neutralizing antibodies against AAVx capsid
- Analytical and clinical performance demonstrated during validation (extent of clinical performance depends on the claimed intended purpose)
- Validation setup should follow CLSI and/or EMA/FDA guidelines

→ **What is different compared to a GCP validation? What can be done the same way?**

Validation Parameters

GCP Validation (FDA/EMA)	IVDR Validation (CLSI)
Cut point	Limit of Blank
Sensitivity	Limit of Detection
Selectivity	Limit of Quantification
Target Interference	Measuring Range
Drug Tolerance	Cross-reactivity
Precision	Interfering substances
Stability	Precision
	Stability
	Trueness
	Carry-Over
Testing a surrogate positive control is accepted	**Actual samples should also be tested**

Approach: Hybrid validation

- Validation parameters were assessed following EMA/FDA and (partially) CLSI guidelines
- Technical Documentation according to Annex II of IVDR was prepared

- Clinical Trial Application was submitted in France
  - No observation was made on the validated method
  - Compliance with IVDR Annex I General Safety and Performance Requirements (GDPR) was accepted
  - France is claiming that ISO15189 accreditation is required
  - Germany claims that ISO15189 accreditation is not required for IVDR and that a CRO is not eligible for accreditation

Conclusions

- Clear guidance on expected scope for IVDR-compliant validations for bioanalytical assays is missing
- A GCP validation can be considered state of the art. Further assessments should not be required for IVDR-compliant validations
- Setup of the validation should be well aligned with all relevant stakeholders
- In our experience, the lab efforts for an IVDR validation are moderately higher than for a GCP validation. A greater amount of work and resources is needed for the Technical Documentation according to Annex II of IVDR

Thank You!

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