IVDR regulations and consideration or application to VCN and vector shedding assays

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EBF Spring Focus Workshop – Malaga June 2024
IVDR: Our Next Challenge?

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Agenda

- Brief overview of study type(s)
  - Vector copy number (VCN)
  - Vector shedding
- Case study 1
- Case study 2

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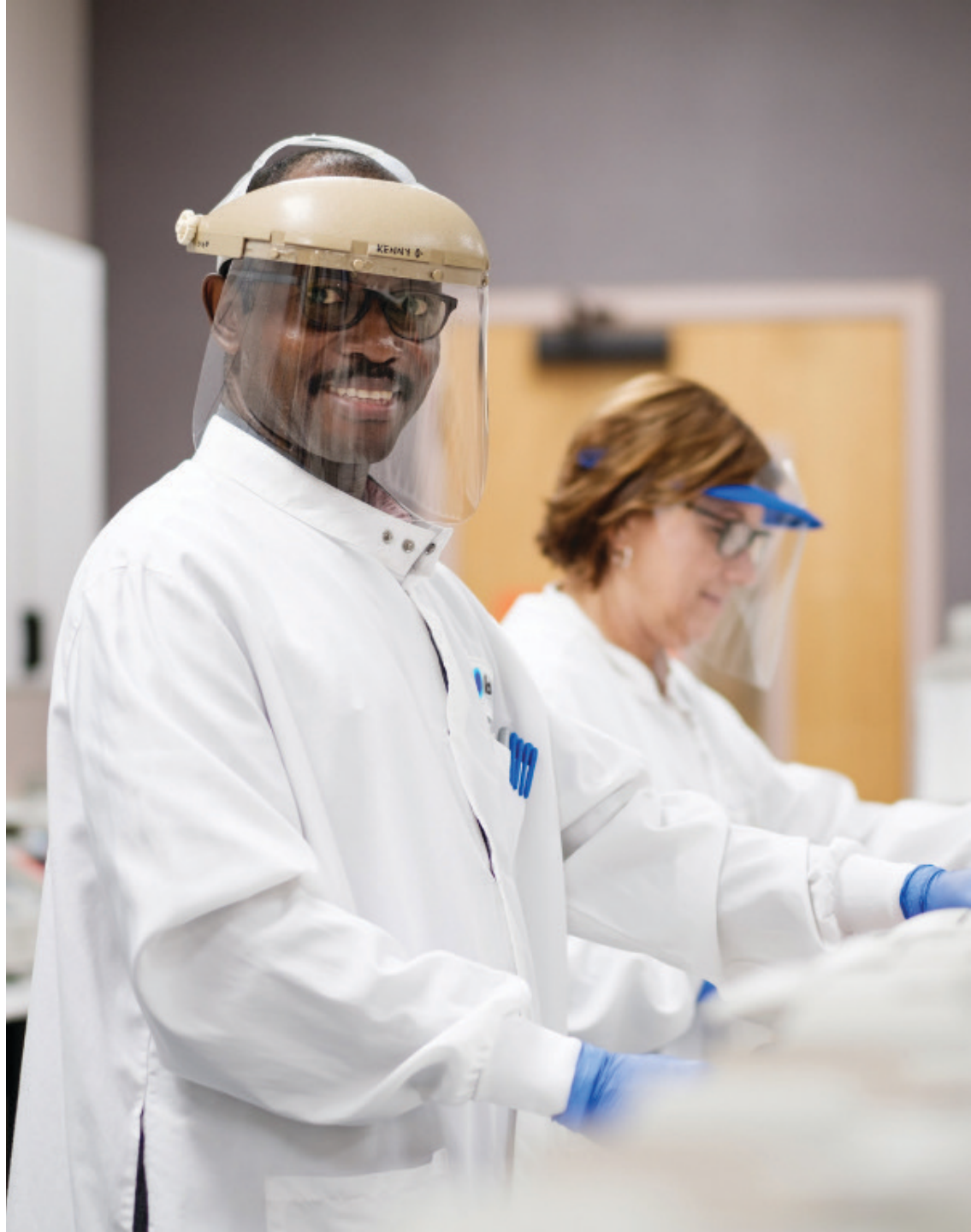
What are VCN and Vector Shedding Studies?

Vector copy number (VCN) assays

What are they?

- Indicates the copy number of therapeutic vector integrated into the target cells
- If VCN is too high, there is increased risk of oncogenesis
  - FDA recommends <5 copies per cell of final product
- Also to monitor CAR-T cell in patient samples following administration
- Within Mol BioA we perform the latter by qPCR/ddPCR on samples
  - Peripheral blood samples
  - Preclinically in tissue samples as well, also possible in clinical setting



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Vector shedding assays

What are they?

- Provide information on likelihood of transmission to untreated population
- Evaluation of transmission prevention
- Mol BioA perform by qPCR/ddPCR in various samples
  - Blood, urine, faeces, sperm, semen, CSF, etc.
  - Preclinically in tissue samples as well

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Case Study 1

Case Study 1 – VCN assay

Clinical trial protocol

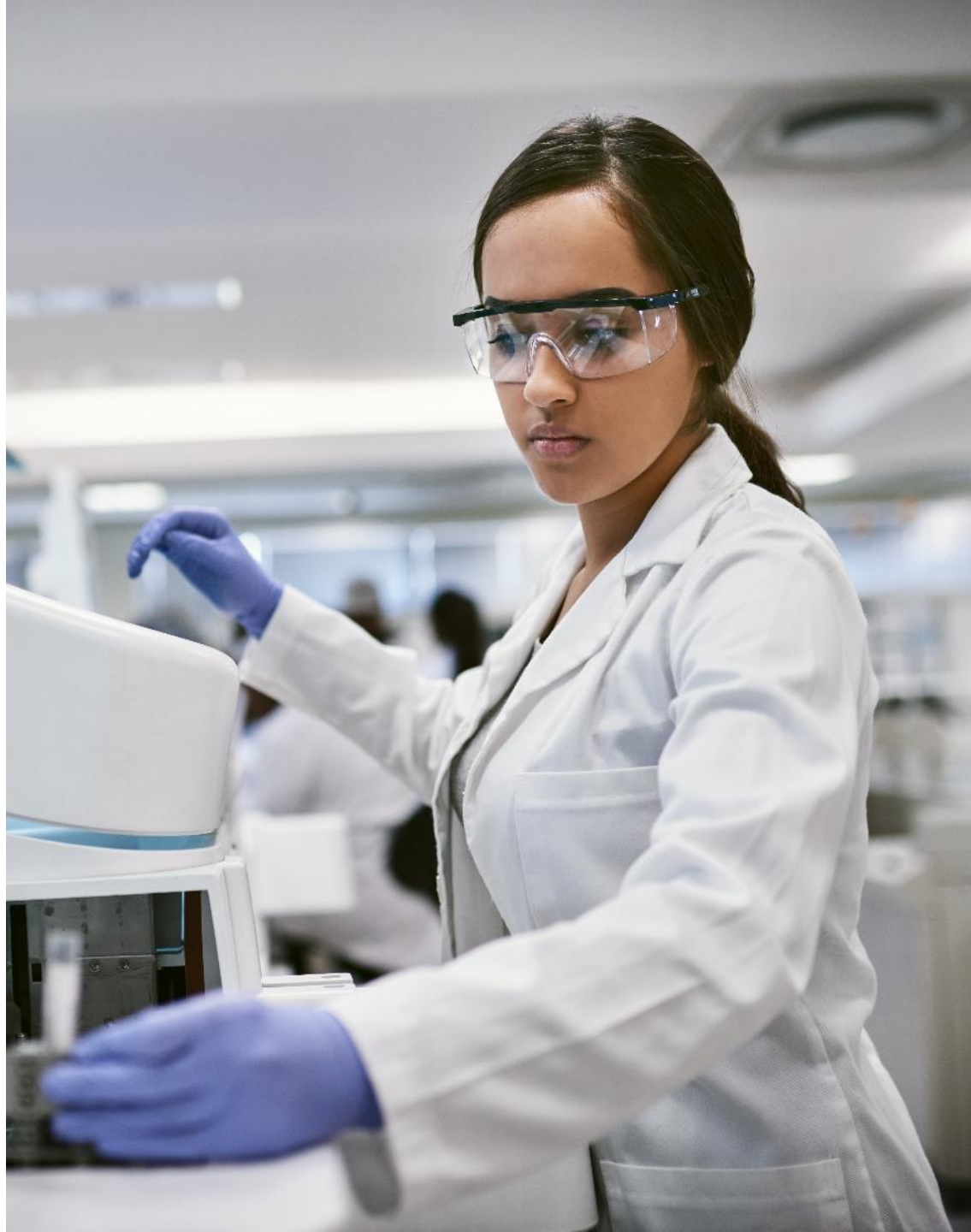
- Primary endpoint
- PIII

Type of material

- Gene therapy consisting of transduced cells
- Intended as a single dose

VCN assay

- Detection of vector target in blood
- One of two indicators for treatment failure
  - Failure if <LLOD
  - Successful if >LLOD
- Other pharmacodynamic effects and physiological indicators
- VCN monitored following administration to patient



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Study setup

- Discussions with Sponsor were on-going for several months prior to clinical trial start
- As primary endpoint and assay was considered being used for patient management IVDR and CLIA required
- Could not achieve CE marked assay
  - Time required to generate a CE marked assay meant other options necessary

Considerations

- Intention of the test
  - Unlikely to be a marketed test
  - Not a diagnostic test
  - Bespoke assay designed for this specifically for this target only
- Gene therapies are single dose
  - No intention of reviewing results and adjusting the dosing regime

Study conduct

Mitigation

- Phase III therefore multisite study when compared to Phase I/II
  - Performed the VCN assay in a CLIA lab for US/Non-EU patients
  - Performed the VCN assay in a medical institute for EU patients
- Ensure assay equivalence at the testing sites

Case Study 2

Case Study 2 – Vector shedding assay

Clinical trial protocol

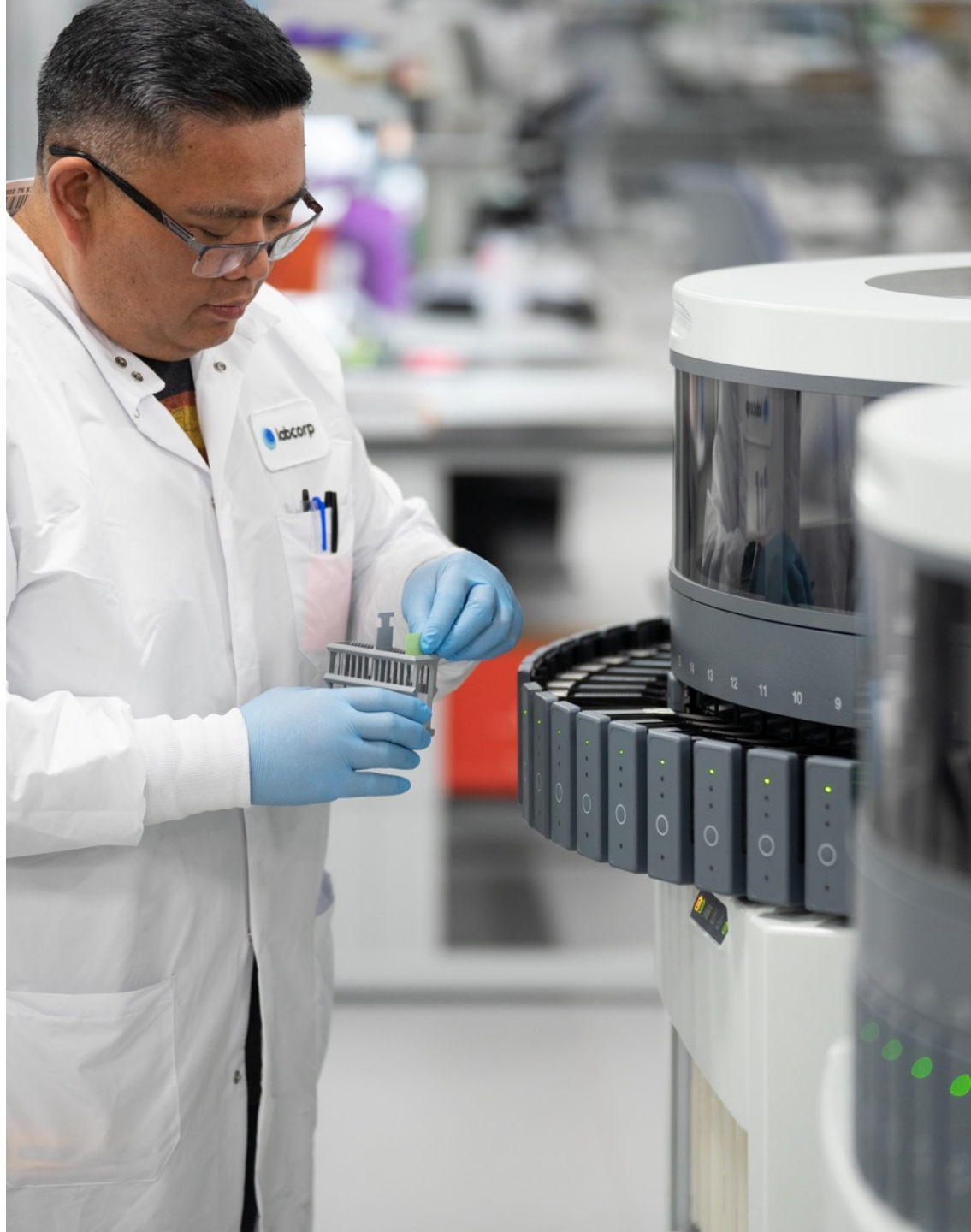
- Safety consideration
- Phase I/II

Type of material

- AAV gene therapy vector expressing a specific gene under a tissue specific promoter
- Intended as a single dose

Vector shedding assay

- Detection of vector target in variety of matrices for safety assessment



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Study setup

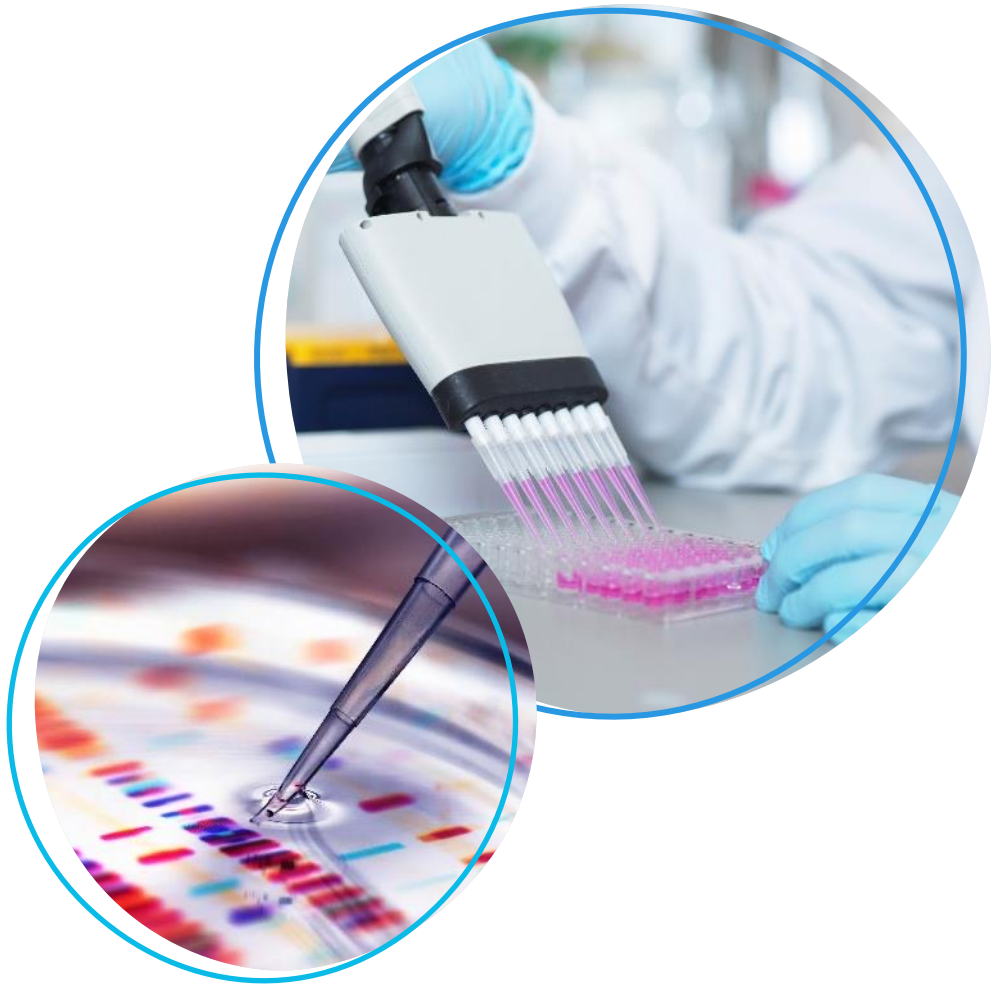
- Clinical trial running for considerable number of years
- Results specifically used to determine if patient should continue contraception and called out in CTP
  - Considered to be patient management
  - CLIA required
- Not primary endpoint or secondary endpoint
- As CLIA, should IVDR therefore now also be applied?

Considerations

- Intention of the test
  - Unlikely to be a marketed test
  - Not a diagnostic test
  - Bespoke assay designed for this specifically for this target only
- Gene therapies are single dose
  - Vector shedding data not used for adjustment of dosing regime

Mitigation

- Phase III therefore multisite study when compared to Phase I/II
  - Performed the VCN assay in a CLIA lab for US/Non-EU patients
  - Performed the VCN assay in a medical institute for EU patients
- Ensure assay equivalence at the testing sites



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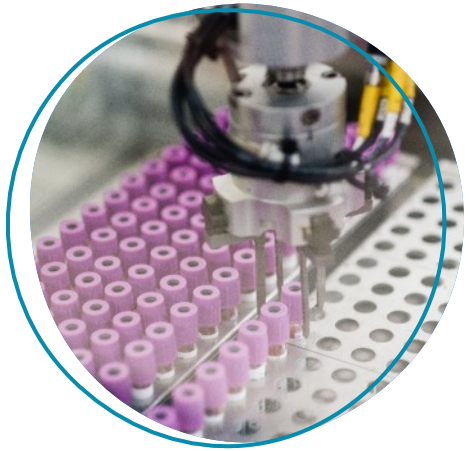
Conclusions

Conclusions



Actual Tests

- Intention of the test
- Not a diagnostic test
- Unlikely to be a marketed test
- Bespoke assay designed for this specifically for this target only
- No marketed alternative
- Cell and gene therapies are generally single dose
- CLIA = IVDR

Data Usage

- CTP written in different ways
- Data not used for adjustment of dosing regime
- Usually combined with other supporting assays or considerations
- Likely to be a smaller number of studies and sample volumes per test compared to diagnostics

Patient Considerations

- At the heart of everything we do
- Investigating process at present
- Discussing with regulators
- Time required and cost obtaining CE marked test
- Slow down clinical trials starting and ultimately increase cost

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Thank you