The IVDR and its Impact on Clinical Immunogenicity Assay Development

Robert Nelson PhD | 23 April 2024

BioAgilytix

Disclaimer

- The views and opinions expressed herein represent our current understanding and interpretation of the topic. They should not be used in place of regulations, regulatory guidelines, or direct discussions with health authorities/notified bodies.

Agenda

1. What is the IVDR and what's in scope?
2. Routes to compliance with the IVDR
3. Impact on immunogenicity assays
4. Concluding remarks

What is the IVDR and what's in scope?

What is the IVDR?

- Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU
  - Shortened to '**in vitro diagnostic medical devices regulation**'
  - Abbreviated to '**IVDR**'

- Published in May 2017, became effective in **May 2022**
  - 205-page document after corrections and amendments
  - Aims to ensure high standards of quality and safety for IVDs and to protect the health of patients and users
  - Strong focus on the documentation, safety and performance requirements to make a test available on the market

The IVDR and bioanalytical laboratories supporting clinical trial assays

- Initially there was little concern, as it appeared that most bioanalytical assays (e.g., PK, ADA, NAb) were out of scope

REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 5 April 2017

on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU

(Text with EEA relevance)

CHAPTER I

INTRODUCTORY PROVISIONS

Section 1

Scope and definitions

Article 1

Subject matter and scope

1. This Regulation lays down rules concerning the placing on the market, making available on the market or putting into service of *in vitro* diagnostic medical devices for human use and accessories for such devices in the Union. This Regulation also applies to performance studies concerning such *in vitro* diagnostic medical devices and accessories conducted in the Union.

The interface of IVDR and clinical trials

- In May 2022 (the month that the IVDR became effective), the Medical Device Coordination Group (MDCG) published a Q&A addressing this topic
  - Became clear that some clinical trial assays were very much in scope
- Assays used for '**medical management decisions**' of trial subjects within the trial
  - Which assays are these?

MDCG 2022-10

Q&A on the interface between Regulation (EU) 536/2014 on clinical trials for medicinal products for human use (CTR) and Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices (IVDR)

May 2022

The interface of IVDR and clinical trials

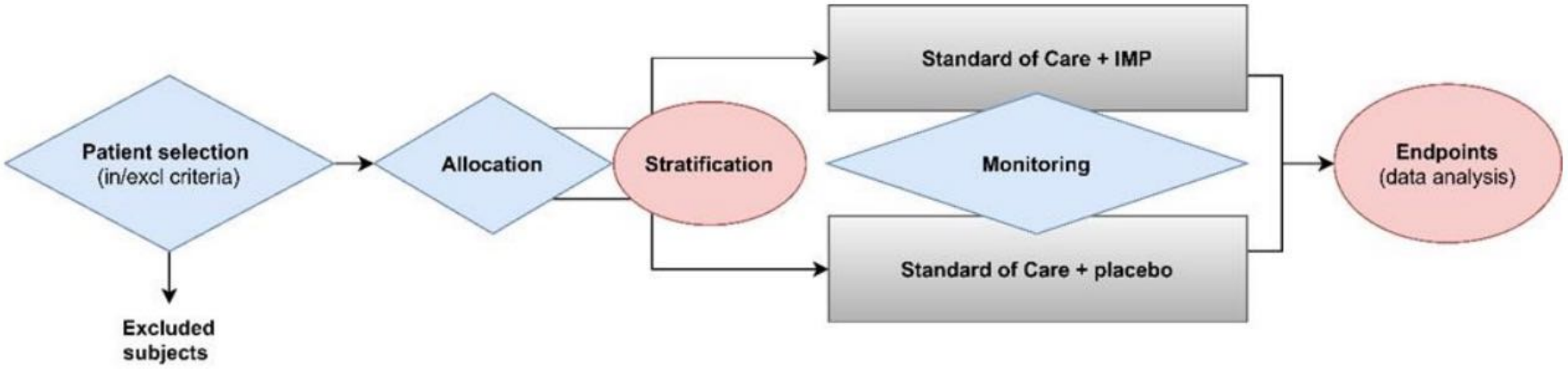

Fig. 1 Simplified examples of use of assays on human samples in a clinical trial. Assays marked in blue (diamonds) are considered to be assays which will likely be considered IVDs as they are used for medical management decisions of trial subjects within the trial. The processes in yellow pink (ellipses) are considered to likely not to impact the medical management of the trial subjects and therefore would not have a medical purpose in the trial.

Source: Medical Device Coordination Group (MDCG) 2022-10. Q&A on the interface between Regulation (EU) 536/2014 on clinical trials for medicinal products for human use (CTR) and Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR). May 2022.

Routes to compliance with the IVDR

Food for thought…

- **“if it’s not in scope, don’t put it in scope”**
  - Timmerman et al. (2024) 16(3), 117–120

Commentary

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Bioanalysis

Finding our way in the *In Vitro* Diagnostic Medical Devices Regulation: a discussion paper from the European Bioanalysis Forum

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> “We observe there is a growing risk of scope creep, i.e., applying IVDR across the board of all clinical studies, e.g., pharmacokinetic, immunogenicity, AAV or biomarker evaluation.”

Pathways to compliance of assays to IVDR

1. Use a test/assay than is CE IVD certified **for that intended use**
   - Open questions on whether such a test can be used in non-EU labs to support testing of EU samples

CE IVD

Opportunities:

- Where a suitable assay exists, may (?) be the simplest pathway

Challenges/Hurdles:

- CE-marked assays are often not for the same intended use
- CE-marked assay may have inferior performance to existing bioanalytical assay
- For many clinical assay endpoints, no CE-marked assay exists

Pathways to compliance of assays to IVDR

2. Use a test/assay that is on its way to CE IVD certification
   - Requires filing of documentation related to IVDR General Safety and Performance Requirements (GSPRs)
   - Assay is formally evaluated under a **Performance Study**

   Opportunities:
   - This may be a suitable pathway when an assay already exists in a non-EU lab

   Challenges/Hurdles:
   - An IVD performance study is no small undertaking (many similarities with a clinical study…)

Pathways to compliance of assays to IVDR

3. Use a test/assay as an '**in house IVD**'
   - Assay is set-up (manufactured) and used only within a single health institution under appropriate quality management systems, no distribution to 3rd parties

   Opportunities:
   - For early clinical assays, provides a path before committing to a full IVD performance study

   Challenges/Hurdles:
   - Limited to single site for analysis
   - May need to move an existing assay to EU lab

Supporting in-house IVD testing

- The test laboratory is a '**health institution**' in the EU
  - MDCG 2023-1#: …health institutions include hospitals as well as institutions, **such as laboratories** and public health institutes **that support the health care system and/or address patient needs, but which do not treat or care for patients directly**.

- Quality Management System (QMS) for the Lab
  - **ISO 15189:2022** compliant processes
  - Also considerations of **ISO 13485:2016** for manufacturing

- Technical documentation according to Annex II of IVDR

Medical Device Coordination Group (MDCG) 2023-1. Guidance on the health institution exemption under Article 5(5) of Regulation (EU) 2017/745 and Regulation (EU) 2017/746. January 2022.

Impact on immunogenicity assays

ADA as an inclusion/exclusion criteria

Compound Type	AAV-based Gene Therapy
Type of Assay	Antibodies against AAV capsid • Total Antibodies (TAb) • Neutralising Antibodies (NAb)
Scope	1) Screen patients for pre-existing antibodies to AAV for inclusion/exclusion purposes → **IVDR** 2) Describing the correlation of immunogenicity with safety and efficacy → **Immunogenicity guidelines**

- How best to approach this for compliance with multiple regulations?

Assay 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	Carry-Over
Precision	Interfering substances
Stability	Precision
	Stability
	Trueness

Limit of blank (LoB) | Cut-point

- According to CLSI EP17-A2
  - Run negative samples over multiple days by multiple operators (at least 60 datapoints)
  - Set a 95% threshold using a non-parametric (e.g., 95th percentile) or parametric approach (e.g., Mean Signal +/- 1.645 x SD) on normalized signals

- Approach for cut-point evaluation following immunogenicity guidelines fulfils requirement

Limit of quantitation & trueness

Limit of quantitation (LoQ)

- LoQ not applicable in a qualitative assay, therefore not determined

Trueness

- Closeness of agreement between the average value obtained from a large series of test results and an accepted reference value
- As there is no reference value available, trueness will not be assessed

Precision

Immunogenicity guidelines

- Assess precision of PCs in at least 6 runs (min. 12 replicates per sample)
  - Involvement of several analysts and analytical instruments recommended

CLSI EP05-A3 Section 3 (Quantitative Measurements)

- For each sample: minimum 20 days, 2 runs per day, 2 replicates per runs (min. 80 replicates per sample)
  - Run this setup with multiple instruments, multiple lots and multiple operators?
  - Could end of with 2 instruments x 2 lots x 2 operators x 80 replicates = 640 replicates per sample…!

Concluding remarks

Concluding remarks

- The IVDR becomes relevant when assays are used for ‘medical management decisions’ of clinical trial subjects
  - e.g., inclusion/exclusion, stop criteria
  - Added complexity for such assays to remain compliant to both IVDR and bioanalytical regulations

- We observe a growing risk of scope creep, with IVDR being (potentially) applied across many different clinical assay endpoints
  - e.g., pharmacokinetic, immunogenicity, or biomarker evaluation

- Need to engage stakeholders to find a path that brings the most value to the patient

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Thank You | Obrigado

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