16th Open Symposium

Science Winning the Race

In the Chicane 2: IVDR, What is the Role for Reg. BioA?

Anna Laurén, on behalf of the EBF

15-17 November 2023, Barcelona

Why discuss IVDR in a bioanalytical meeting?

- In vitro diagnostic medical devices regulation (IVDR) is setting new requirements in EU for analytical tests that are used for patient management.

- In scope: Results from individual study participants that are reported to sites/investigator (*used for patient treatment decisions).*
- Not in scope: Results from individual study participants that are not reported to sites/investigator (e.g., standard PK/immunogenicity).

- EBF members have highlighted issues in interpretation of the IVDR scope
- Previous EBF discussions: EBF Focus workshop September 2022
  AAPS OSD June 2023,
  Reid Forum, September 2023

"If not in scope, don't put it in scope."

Todays agenda

- Short introduction to IVDR
- Present surveys from the EBF team
- Discussion around tables
- Wrap-up

The EBF team since May 2023

- Diana Steinbuesch, F. Hoffmann - La Roche
- Eginhard Schick, F. Hoffmann - La Roche
- Mario Richter, Abbvie
- Philippe Ancian, Charles River Laboratories
- Antje Lukas, Boehringer-Ingelheim
- Louis Christodoulou, UCB
- Tracy Iles, Labcorp
- Claire Seal, F-star, an invoX company
- Petra Struwe, Celerion
- Lene Andersen, Lundbeck
- Robert Nelson, BioAgilytix
- Yang Liu, Novartis
- Janet Waldron, Novartis
- Monika Köhnke, BioAgilytix
- Anna Laurén, Novo Nordisk

A mix of different roles

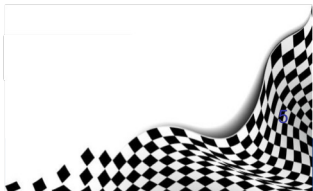
- Head of Bioanalysis
- Bioanalysis Scientists
- Biomarker Scientists
- Precision Medicine Leads
- BioSample Operations
- IVD experts
- QA

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

191 pages, 84000 words…



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.

2. For the purposes of this Regulation, *in vitro* diagnostic medical devices and accessories for *in vitro* diagnostic medical devices shall hereinafter be referred to as 'devices'.

3. This Regulation does not apply to:

(a) products for general laboratory use or research-use only products, unless such products, in view of their characteristics, are specifically intended by their manufacturer to be used for *in vitro* diagnostic examination;

(b) invasive sampling products or products which are directly applied to the human body for the purpose of obtaining a specimen;

(c) internationally certified reference materials;

(d) materials used for external quality assessment schemes.

4. Any device which, when placed on the market or put into service, incorporates, as an integral part, a medical device as defined in point 1 of Article 2 of Regulation (EU) 2017/745 shall be governed by that Regulation. The requirements of this Regulation shall apply to the *in vitro* diagnostic medical device part.

5. This Regulation is specific Union legislation within the meaning of Article 2(3) of Directive 2014/30/EU.

6. Devices which are also machinery within the meaning of point (a) of the second paragraph of Article 2 of Directive 2006/42/EC of the European Parliament and of the Council ([22]) shall, where a hazard relevant under that Directive exists, also meet the essential health and safety requirements set out in Annex I to that Directive to the extent to which those requirements are more specific than the general safety and performance requirements set out in Chapter II of Annex I to this Regulation.

7. This Regulation shall not affect the application of Directive 2013/59/Euratom.

8. This Regulation shall not affect the right of a Member State to restrict the use of any specific type of device in relation to aspects not covered by this Regulation.

9. This Regulation shall not affect national law concerning the organisation, delivery or financing of health services and medical care, such as the requirement that certain devices may only be supplied on a medical prescription, the requirement that only certain health professionals or health care institutions may dispense or use certain devices or that their use be accompanied by specific professional counselling.

10. Nothing in this Regulation shall restrict the freedom of the press or the freedom of expression in the media in so far as those freedoms are guaranteed in the Union and in the Member States, in particular under Article 11 of the Charter of Fundamental Rights of the European Union.

Scope and subject matter

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.

Scope: IVDs in European Union

Consider IVDR in a clinical study or after submission?

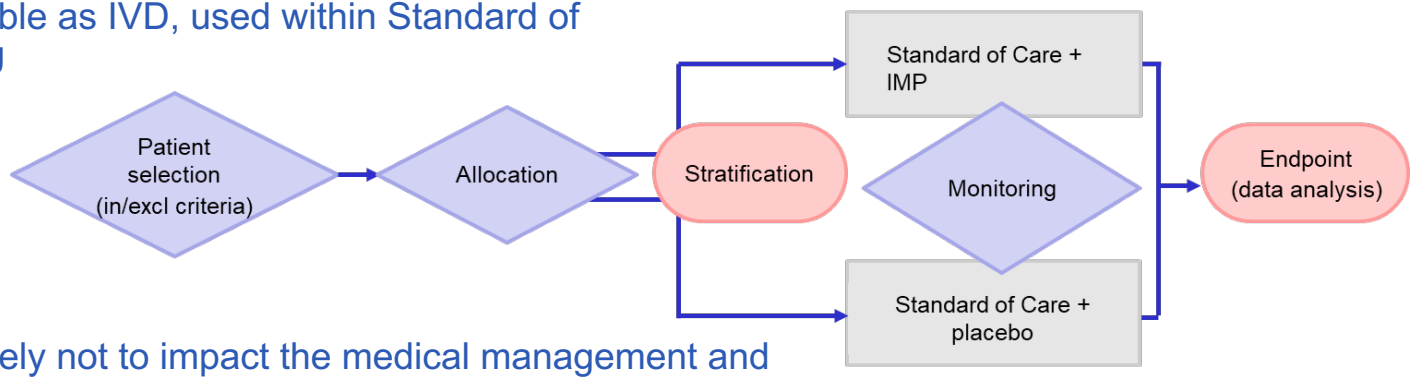
Article 2 Definition 46:

- ‘Interventional clinical performance study’ means a clinical performance study where the test results may influence patient management decisions and/or may be used to guide treatment.

Consider IVDR in a clinical study or after submission?

*Guidance - MDCG endorsed documents and other guidance **(europa.eu)** :*
Medical Device Coordination Group Document MDCG 2022-10

: assays which will likely be considered IVDs as they are used for medical management decisions of individual trial participants.
Consider if tests available as IVD, used within Standard of care/Intended use/CoU

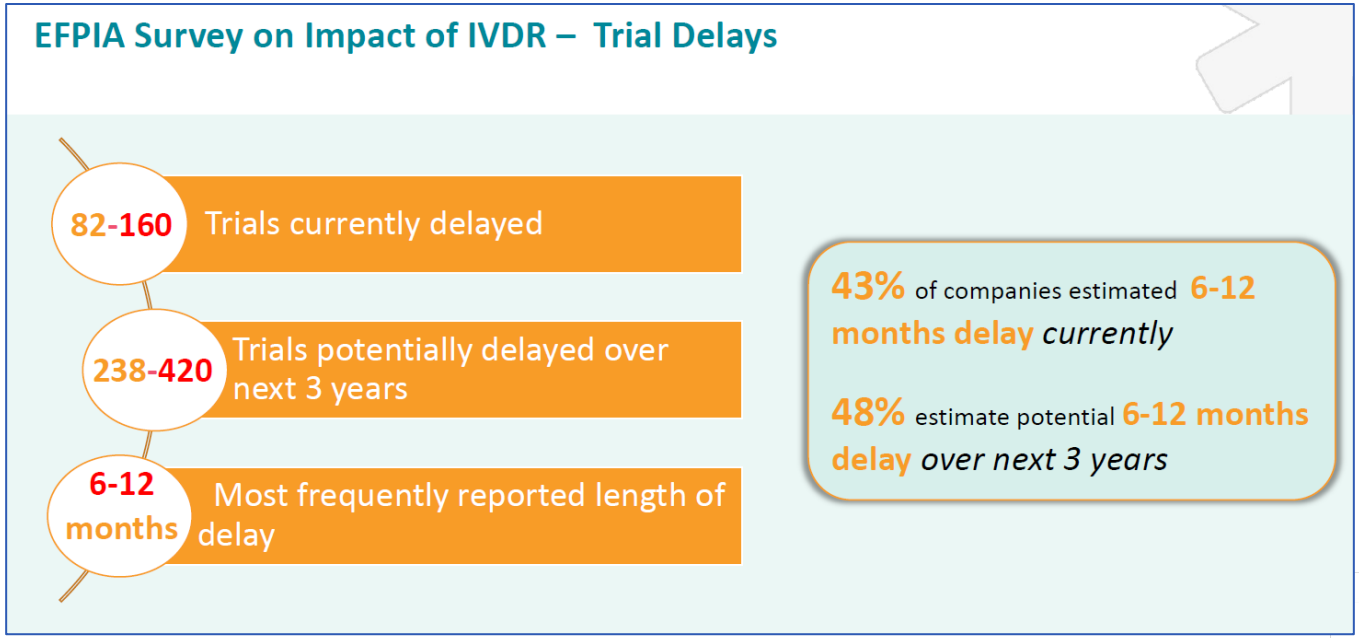


: Considered likely not to impact the medical management and IVD not needed.
Stratification assays may end up as IVDs in future clinical trials (e.g., used for allocation or monitoring)

"If not in scope, don't put it in scope."

EBF are not alone: EFPIA statement June 2022

- Limited information for IVDs used in clinical trials.
- No supportive infrastructure and guidance are in place.



EFPIA survey on impact for clinical studies: efpia_ivdr-survey-slides.pdf
EFPIA statement on impact for clinical trials: EFPIA statement on the concerning impact of the In Vitro Diagnostic Regulation

When IVD is in scope

Analytical Method Requirements for Patient Management and Diagnostics

US

- IVD classification in risk class I-III
- Class III diagnostic tests must be approved for marketing by FDA
- Class I and II diagnostic tests are exempt of 510(k)

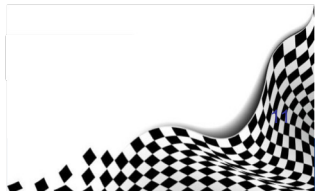
- Laboratory developed tests (LDTs)
  - Validated according to their intented use in CLIA-certified laboratories
  - Under oversight of Centers for Medicare & Medicaid Services
  - October 2023: FDA Notice on new rule for registration requirements for LDT. Most likely effective after 2028.

510(k) Premarket Notification (fda.gov)
Device Classification Under Section 513(f)(2)(De Novo) (fda.gov)
https://www.federalregister.gov/documents/2023/10/03/2023-21662/medical-devices-laboratory-developed-tests

European Union

- Before May 2022: EU Directive applied to medical devices (MD) and in vitro diagnostics (IVDs) since the 1990s for CE labelling
- May 2022: New in vitro diagnostic medical devices regulation (IVDR) - Regulation (EU) 2017/746
- Four risk classes D, C, B, and A
- Grace period until 2025 for high-risk class D devices currently registered under IVD
- The IVDR lays down rules concerning:
  - scientific validity, analytical performance, clinical performance
  - “making available on the market” or “putting into service”
- Scope includes in-house IVD (= EU equivalent to LDT in US)

Q&A: New In Vitro Diagnostic Medical Devices Regulation (europa.eu)
https://www.medtecheurope.org/
Guidance - MDCG endorsed documents and other guidance (europa.eu) : Medical DeviceCoordination Group DocumentMDCG 2022-10



Accreditation standards for diagnostic laboratories

CAP/CLIA	ISO 15189:2012
US Federal Law	International Standard used in EU
Scope: Testing of US patients with focus on individual clinical treatment, medical diagnosis, or disease prevention	Scope: Focus on competence of health institutions conducting testing, e.g. medical and hospital laboratories #
If testing facility in clinical studies intends to report out US patient-specific results to an investigator, testing falls under CLIA*. Laboratory tests accepted (LDT).	International, national, or regional regulations or requirements may apply to specific topics covered in this Standard. In-house IVD accepted.
Participation in Proficiency Testing (PT) (external laboratory control)	Participation in External Quality Control (EQC) programs = PT

** Out of scope: Laboratories that test human specimens but do not report patient-specific results to a health provider. Confirmed by CMS CLIA LabExcellence*

 # ISO 17025:2017 specifies the general requirements for the competence, impartiality and consistent operation of laboratories

Focus on Data Integrity is different to GCP and very limited focus on Archive of Raw Data

"If not in scope, don't put ISO/CLIA in scope"

Terminology in IVD that confuses stakeholders

Term	Approval status	Definition
Approved IVD	CE-marked, FDA clearance and/or relevant national approval.	IVD approved and used within its approved intended use and indication for use. Includes assays used for safety monitoring.
Investigational IVD	Under “Marketing authorisation” (in all study countries).	A new IVD, or an existing IVD used outside approved intended use, being assessed for clinical performance or safety, possibly for device approval procedure.
Research use only test (RUO)	N/A	*Tests used for research purposes, in feasibility or pre-clinical studies, not yet under design control and GMP.*

IVD mindset: PK, Biomarker and Immunogenicity are RUO assays since no validation according to IVD requirements.

*Drug development: PK, Biomarker and Immunogenicity assays used for Pivotal studies for submissions are **”Regulated validated assays”.***

In-house tests can be used for IVD/investigational IVD

- ‘In-house IVD’ definition according to IVDR:
  - Manufactured and used within the same health institution.
  - Not marketed or transferred to other legal entities.
  - Do not bear the CE marking.
  - Can be essential for the diagnosis and treatment, especially for rare diseases.

- In-house devices are exempted from the IVDR, when the Health institution meets a number of conditions set out in Article 5(5) of the Regulation:
  - Appropriate quality management system.
  - Comply with requirements for medical laboratories (EN ISO 15189) or other national provisions.
  - Document justification that target patient group's specific needs cannot be met by an equivalent marketed IVD available on the market.
  - Public declaration about device and intended use.
  - Documentation must be provided upon request by competent authorities.

Q&A: New In Vitro Diagnostic Medical Devices Regulation (europa.eu)
MDCG 2023-1 Guidance on the health institution exemption under Article 5(5) of Regulation (EU) 2017/745 and Regulation (EU) 2017/746
Experience With IVDR Implementation in Three Diagnostic Laboratories: Messages to EU Health Institutions, Diagnostic Healthcare Payers, and Authorities. (2023) 7:4

EBF members experience in IVDR related questions

EBF core members experience in IVDR related questions

50 responders

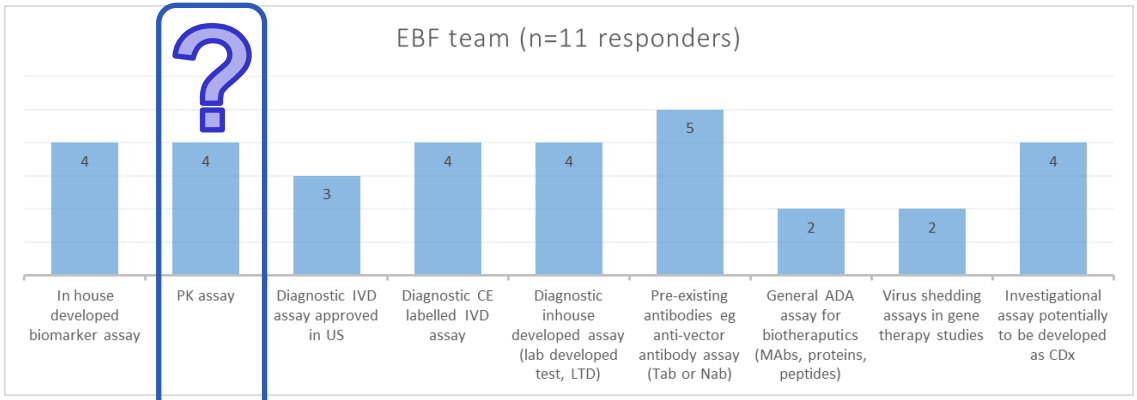
Pharma	29
CRO	21

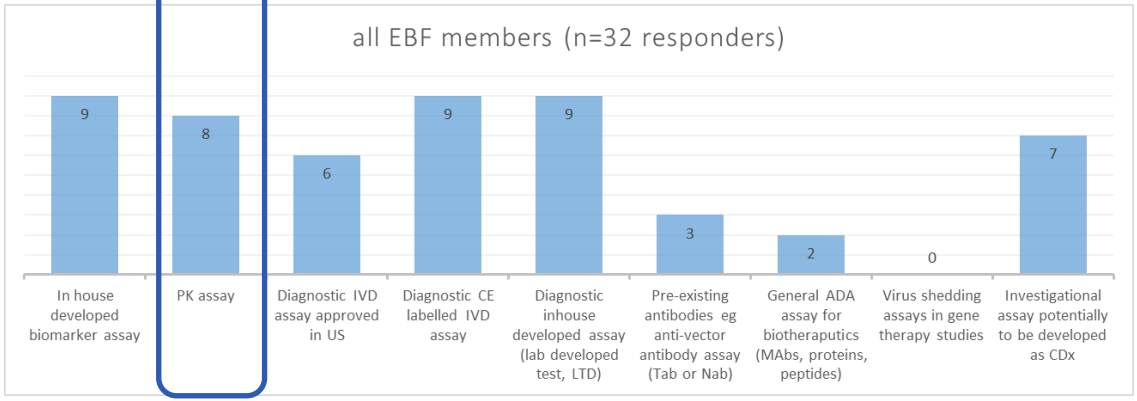
Bioanalytical scientist	29
Biomarker assay scientist	4
Biomarker lead/Translational lead	1
Regulatory/Precision medicine	0
Other	20

Have you experienced IVDR related discussions/questions within you function for assays used for patient management decisions?

Yes	
No	

What type of assays have you discussed?





PK?

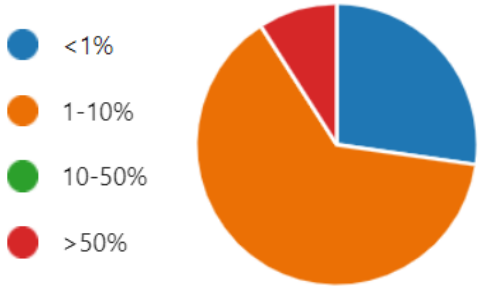
Only 6 companies:
- 2 CRO/4Pharma

Comments on PK:
- One rare case PK range related to safety in patients = CDx
- It was clarified that PK assay doesn't fall under IVDR regulation.
- Some Sponsors ask if we consider the need for IVD for PK assays for dose escalation: answer is NO!

"If not in scope, don't put it in scope."

Questions discussed within the EBF team

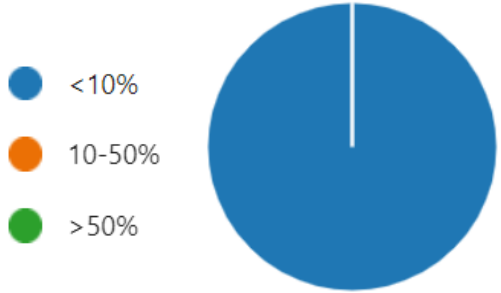
How many assays are impacted out of the total number of assays within your functions responsibility?



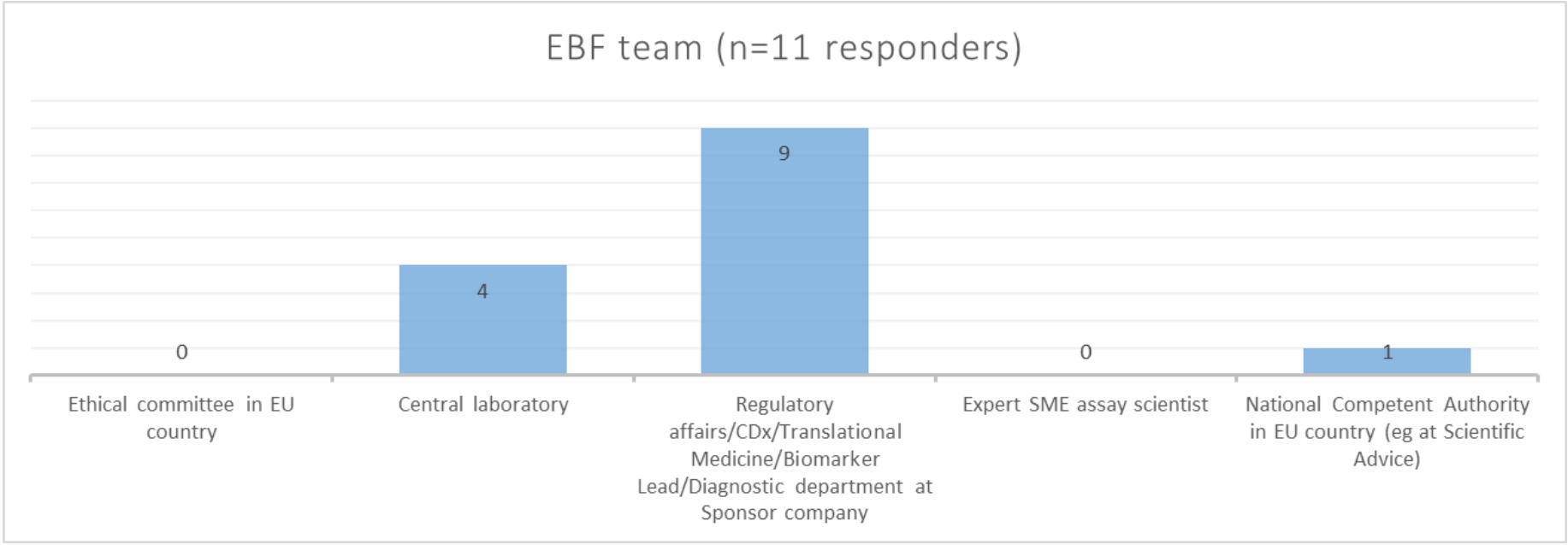
>50% for Translational Lead

Was clinical studies stopped/on-hold/delayed due to IVDR questions/discussions?

How many studies approximately are/was impacted our company?



Who initiated the discussions?



What did the IVDR related questions lead to? Give examples

No impact	Change in trial design	Change in analytical set up	Other
No questions, it was clear what the intended use was from the beginning	Removed test from the study in EU patients (n=2)	Delayed Study start in EU until CE marked assay was validated	Potential discontinuation of IVD products
	Performed the study outside EU	Validations of CE marked alternatives	
	Reporting of individual results for study participant to investigator was not done (n=2)	Found clinical laboratory with ISO15189	
	Ensure that for global studies, EU patient's samples are analysed on a CE marked assay, in EU labs, and also in US labs	Study was initiated with test as investigational assay/device (n=2)	

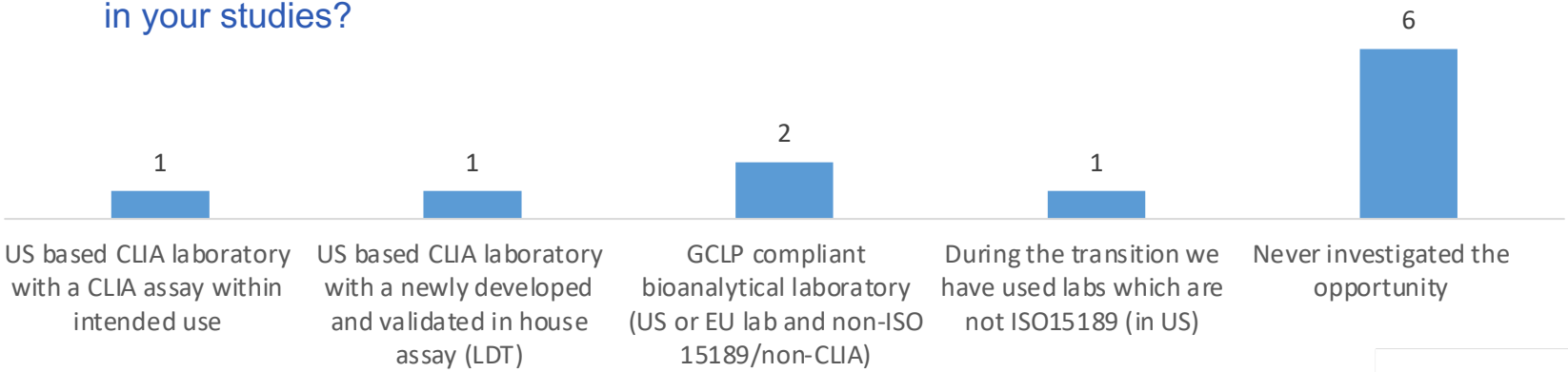
EBF Member Case Story on critical delays for patients: "An US lab is a preferred provider of a very large clinical CRO contracted for a clinical study (full service). CRO contracted a test to the US lab even though the clinical conduct is done only in Europe. Realisation that tests, which is very critical to the study, needs to be moved to a lab in Europe. Clinical CRO process to evaluate new service providers might take up to 6 months!"

EBF team and expected timelines for approval of investigational device application in EU?

- Approved by ethical committe as part of a study protocol.
- Applicable in clinical studies when:
  - IVD is used for patient management outside the intended use.
  - Investigational device is included in a clinical study.
- Recommendation is to use diagnostic regulatory support within you company or outside your company.
- Expected timelines for approval of protocol from ethical committee?
  - Dependent on country
  - From 2 to 12 months?

Which laboratories can be used for IVD testing in EU?

- *Health institutions must have an appropriate quality management system, comply with the international standard setting out the quality and competence requirements for medical laboratories (EN ISO 15189) or other national provisions.*
- Inspiration from Diagnostic laboratories/IVDRArticle 5(5)b,c: Unless specifically required by your member state, accreditation is not strictly necessary, but it is good to be aware that external audits are a sound basis for improving a QMS.
- Have you been able to use a non-ISO15189 laboratory for the assays in scope of IVDR in your studies?



Depending on EU country ISO15189 is not required for IVDs.

The New EU Regulation on In Vitro Diagnostic Medical Devices: Implications and Preparatory Actions for Diagnostic Laboratories. Hemasphere. 2021 May; 5(5)

Wrap up

- In vitro diagnostic regulation (IVDR) is setting new requirements in EU for analytical tests that used for patient management.
- We should prevent scope creep and the consequences thereof.
- EBF will continue the dialogue:
  - A team in the EBF
  - Collaboration outside the EBF
  - An upcoming discussion paper "*Finding our way in the IVDR – a discussion paper from the European Bioanalysis Forum*" currently ready for submission to J. Bioanalysis

"If not in scope, don't put it in scope."

Acknowledgements

The EBF IVDR team
The EBF community
The AAPS community
The Open Symposium Delegates

Contact Information

Questions: info@e-b-f.eu

European Bioanalysis Forum vzw
www.e-b-f.eu

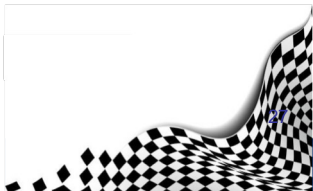
Round Table discussions 17:00-18:00

- 3 topics
  - "If not in scope, don’t put it in scope.“ Dialogue with stakeholders.
  - Do our Bioanalytical community understand scope of IVDR?
  - ”In rare occasions IVDR is in scope”: Role of BA/BM scientist?

- Group into 4 groups: each with one note taker from the EBF team.
- ~ 1700-1730: 10 minutes for each topic.
- ~ 1730-1800: EBF team member summarise discussions from each group.

Part 1 *"If not is scope, don't put it in scope."*

- How many have experienced IVDR discussions?
  - Yes or No?
- Who initated discussions? Examples below:
  - Ethical committee in EU country
  - Central laboratory
  - Regulatory affairs
  - Translational Medicine
  - Biomarker Lead
  - Diagnostic department at Sponsor company
  - Expert SME assay scientist
  - National Competent Authority in EU country (eg at Scientific Advice)
- How can we have a dialogue with our stakeholders about IVDR within drug development?
  - Meetings and workshops?
  - Publish a Decision tree?
  - Other suggestions?



Part 2 *Do our Bioanalytical community understand scope of IVDR?*

- Understanding the scope of IVDR: Is IVDR in scope of?
  - Dose escalation?
  - Individual data reported to site/investigator?
  - Management of individual participants?
  - Other examples?
- Understanding Intended Use and Context of Use of assays? When is IVD needed for?
  - In house developed biomarker assay
  - Commersial kit of a biomarker (RUO status)
  - PK assay
  - Diagnostic IVD assay approved in US
  - Diagnostic CE labelled IVD assay
  - Diagnostic inhouse developed assay (lab developed test, LTD)
  - Pre-existing antibodies e.g., anti-vector antibody assay (Tab or Nab)
  - General ADA assay for biotheraputics (MAbs, proteins, peptides)
  - Virus shedding assays in gene therapy studies
  - Investigational assay potentially to be developed as CDx
  - Other examples?

Part 3 *”In rare occasions IVDR is in scope”*

- Role of bioanalytical/biomarker/immunogenicity scientist when IVDR is in scope?
  - What is needed for the bioanalytical community?
- Inspiration for solutions? Alternative routes? Issues?
  - Avoid recruitment in the EU/US?
  - Need to report PK/ADA/BM for individual patients to investigator?
  - Removed test from the study in EU patients?
  - Validations of CE marked alternatives in EU lab?
  - Include test as investigational assay/device ion the study?
  - Ensure that for global studies, EU patient's samples are analysed using IVD assays in EU and US labs?
  - Other?
- What needs to be fulfilled to be able to act as a health institute within terminology of the IVDR and performing sample analysis for GCP studies?
  - Can a bioanalytical lab with GCP/GCLP QMS be used?
  - Can labs outside EU be used?
  - Is ISO15189 a must?
  - Is CLIA equivalent to ISO15189?