

Autumn Focus Workshop
Biomarkers/CoU - Sharing Experience through Examples

Spotlight on CLIA and recent IVDR – when is it relevant for biomarkers and COU?

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29-30 September 2022 – Malaga, Spain

Why discuss CLIA and recent IVDR

Let us use BM assay results to include patients in study



Can we change dosing of our drug in individual patients based on BM results



Investigator is highly interested in the BM results of his patients, let us share individual data with him



Stakeholders

Is there something I should be aware of?

This is not my responsibility

How will this impact my work?



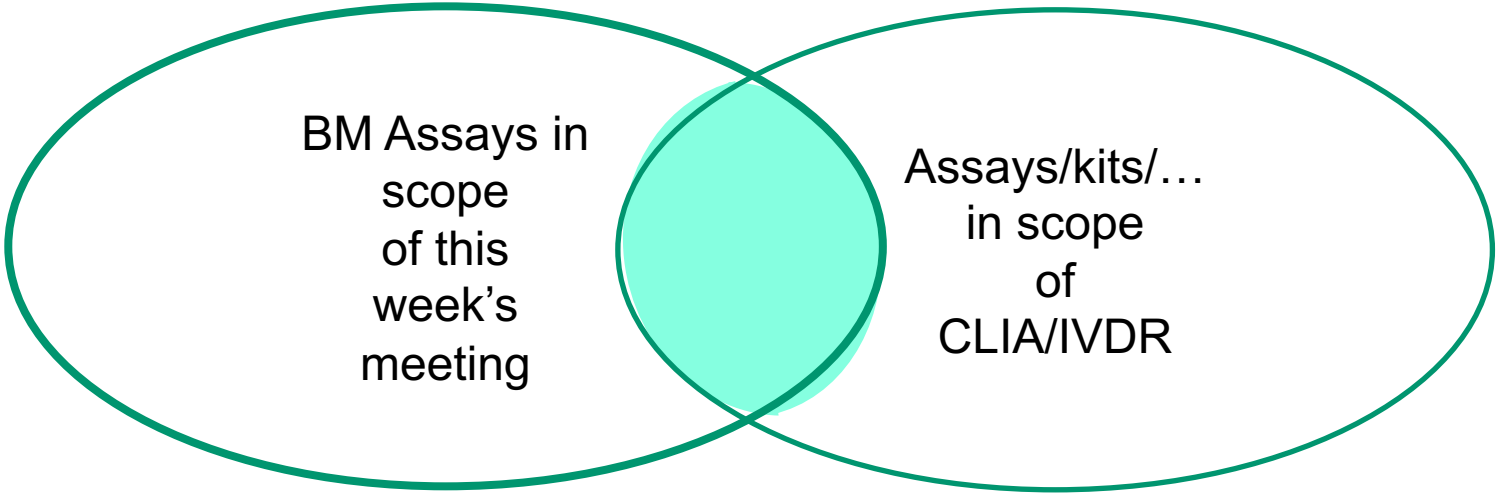
BM scientist

CLIA and recent IVDR

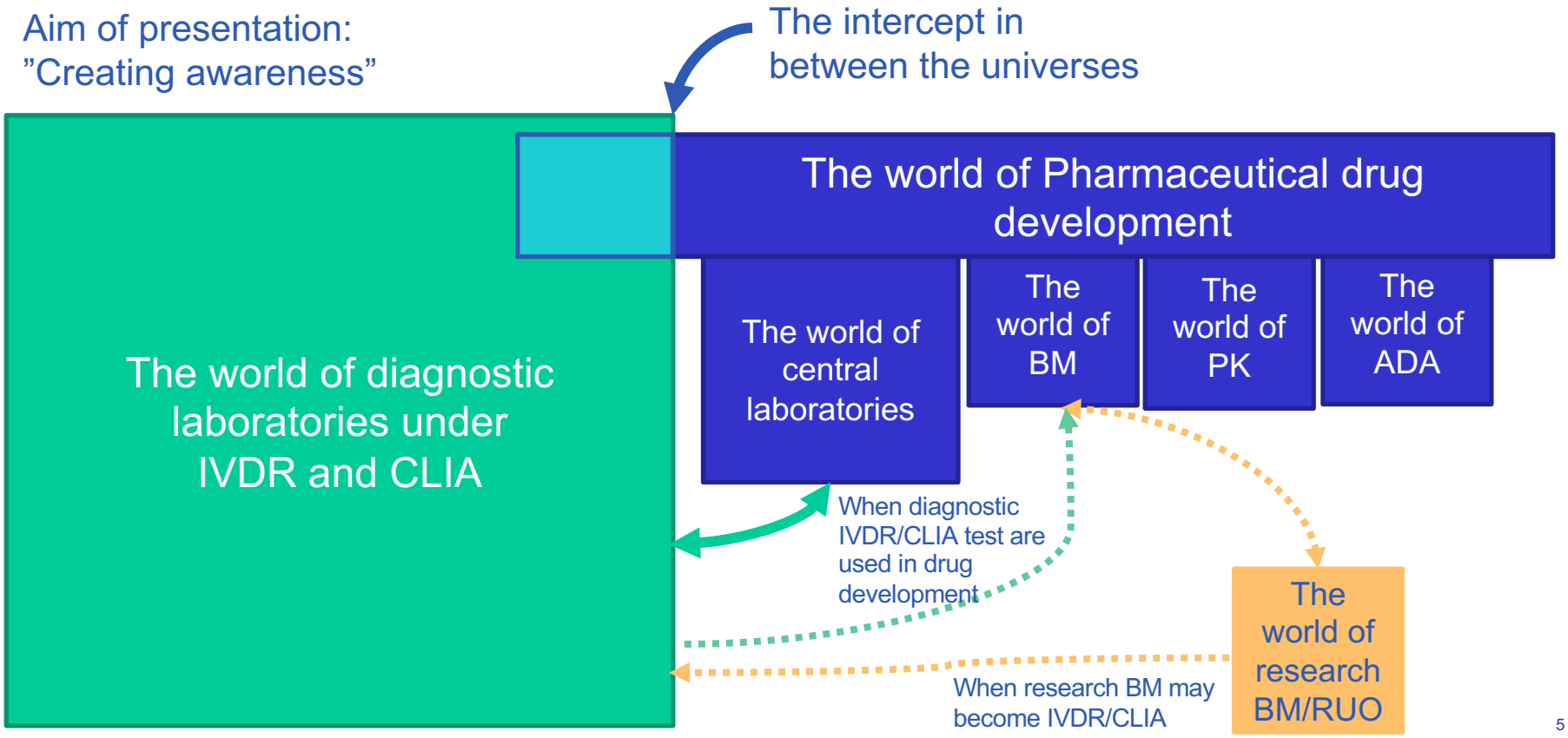
- Spotlight: Introducing requirements that may or may not be relevant in clinical studies and beyond
- Recap: How laboratories most often are involved in clinical studies
- Introducing differences and similarities for
  - Clinical diagnostic laboratories
    - Clinical Laboratory Improvement Amendments (CLIA)
    - ISO 15189:2012 certification
  - In vitro diagnostic directive (IVDD) transition to In vitro diagnostic regulation (IVDR)
  - Companion diagnostics (CDx)
- Discussion: Shall the Bioanalytical and Biomarker scientists be involved?

Being aware of the different universes

- BM considerations may fall in the CLIA/IVDR regulations decisions
- Context of Use (CoU) is a valuable tool to consider when BM assays may fall under CLIA



The laboratory universes for analysing human samples



GCP and EMA Reflection Paper on guidance for laboratories that perform the analysis or evaluation of clinical trial samples

Managing GCP in Regulated Bioanalysis was discussed in details at EBF autumn workshop 15-16 September 2022

Quality assurance and Quality control:

- In-process quality control procedures
- Quality assurance audits
- Analysis in accordance with the principles of GCP
- Trial data is recorded and reported accurately, legibly, completely and in a timely manner
- Trial data is archived

Method validation:

- In all but exceptional circumstances*, analysis should be performed using appropriately validated methods
- ...clude defined acceptance criteria, where ap...te
- The valid... of methods should be documented an...ed
- Relevant storage stabil... must be available if samples are to be ...prior to analysis
- Consider:
  - Appropriate quality control (QC) samples
  - Analytical factors that may potentially affect clinical trial results

A fit for purpose validation is acceptable

* *Where the validation of a method is one of the clinical trial objectives*

Always consider context of use for method validation

To understand what the data will be used for and expected analytical variability

Bioanalytical method validation and study sample analysis

CoU/Scope of guidelines (ICH M10):
Chemical and biological drug quantification and their application in the analysis of study samples

Developing and Validating Assays for Anti-Drug Antibody Detection

CoU/Scope of guidelines (EMA/FDA/Chinese NMPA):
Immunogenicity Testing of Therapeutic Protein Products

Biomarkers,CGT, qPCR, Flow Cytometry, Elispot etc.

COU:
To ensure the appropriate interpretation of data to serve patients.
To understand the scientific or safety decisions taken, expected measured concentrations and changes

These guideline/recommendations do not apply to the development of kits that are intended for point-of-care patient diagnosis (e.g., companion or complimentary diagnostic kits)

Clinical Medical Diagnostic Laboratories

Requirements for Clinical Medical Diagnostic Laboratories:

Diagnostic tests must be validated for it's intended use (CoU)

Operation shall be under a Quality management system (CLIA or ISO 15189:2012 certification, or equivalent)

Research labs by KOL Dr X or Professor B are not in scope

Clinical Chemistry Laboratories

Local Labs

Sample collection and Point of Care tests

Compare to Clinical Study sample analysis: Equipment/methods are similar to Central laboratories and safety laboratories

Special Laboratories

Compare to Clinical Study sample analysis: Equipment/methods can be similar to Bioanalytical and Biomarker Labs

Examples:

- Pathology
- Genetic testing
- Microbiology
- Immunology
- Various Esotheric tests

Technologies: Fully automated to manual: Point of Care, Clinical analysers, MS, LC-MS, immunoassays, PCR, flow cytometry, immunohistochemistry….

A simplified view – laboratories are organised differently in different countries

Accreditation standards for diagnostic laboratories

CLIA

US federal law

Scope: Testing of US patients with focus on individual clinical treatment, medical diagnosis, health assessment or disease prevention

If testing facility in clinical studies intends to report out US patient-specific results to an investigator testing falls under CLIA*

Participation in Proficiency testing (external laboratory control)

** 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 15189:2012

International Standard

Scope: Focus on competence of medical laboratories #

International, national, or regional regulations or requirements may apply to specific topics covered in this International Standard

Participation in external quality control programs

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

Certification both CLIA and ISO can be applied international
Other regional certifications/regulations are also available

Analytical methods used by accreditited laboratories

US and CLIA laboratories

- CLIA approved methods at different complexity levels
- CLIA approved tests for marketing
  - premarket approval application or 510(k)
  - de novo classification request
- Laboratory developed tests (LDT) US term /In-house IVD (EU term) are accetable if laboratory provider has validated test for it's intended use

European Union

- Before May 2022: EU Directive have applied to medical devices (MD) and in vitro diagnostics (IVDs) since the 1990s
  - CE labelled tests approved for marketing
    - self certification under IVDD not possible under IVDR anymore
  - Laboratory developed tests (LDT) were acceptable if laboratory provider has validated test for it's intended use/context of use
- A new in vitro diagnostic medical devices regulation (IVDR) entered into force on 26 May 2022 - Regulation (EU) 2017/746 – grace period until 2025 for high risk devices
  - The IVDR lays down rules concerning:
    - scientific validity
    - analytical performance
    - clinical performance
  - → in order to obtain clinical evidence
  - "making available on the market" or "putting into service"
  - Scope include Laboratory developed tests (LDT)

510(k) Premarket Notification (fda.gov)
Device Classification Under Section 513(f)(2)(De Novo) (fda.gov)

https://www.medtecheurope.org/
Guidance - MDCG endorsed documents and other guidance (europa.eu) : Medical DeviceCoordination Group DocumentMDCG 2022-10

Is the IVDR relevant for new therapeutic drugs?

IVDR scope

- Intended by the manufacturer to be used *in vitro* for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:
  a) concerning a physiological or pathological process or state
  b) concerning congenital physical or mental impairments
  c) concerning the predisposition to a medical condition or a disease
  d) to determine the safety and compatibility with potential recipients
  e) to predict treatment response or reactions
  f) to define or monitoring therapeutic measures

- IVDR scope cover both commercial diagnostic products (CE (Conformité Européenne) mark-labelled) as well as In-house IVD
- In-house IVD or Laboratory developed test (LDT): An IVD manufactured and used within the same health institution
- EFPIA opinion on IVDR: There are still critical challenges to address when it comes to clinical trial initiation in Europe for therapies that require the use of an in vitro diagnostic (IVD) in a trial

EFPIA statement on the concerning impact of the In Vitro Diagnostic Regulation
Guidance - MDCG endorsed documents and other guidance (europa.eu) : Medical DeviceCoordination Group DocumentMDCG 2022-10

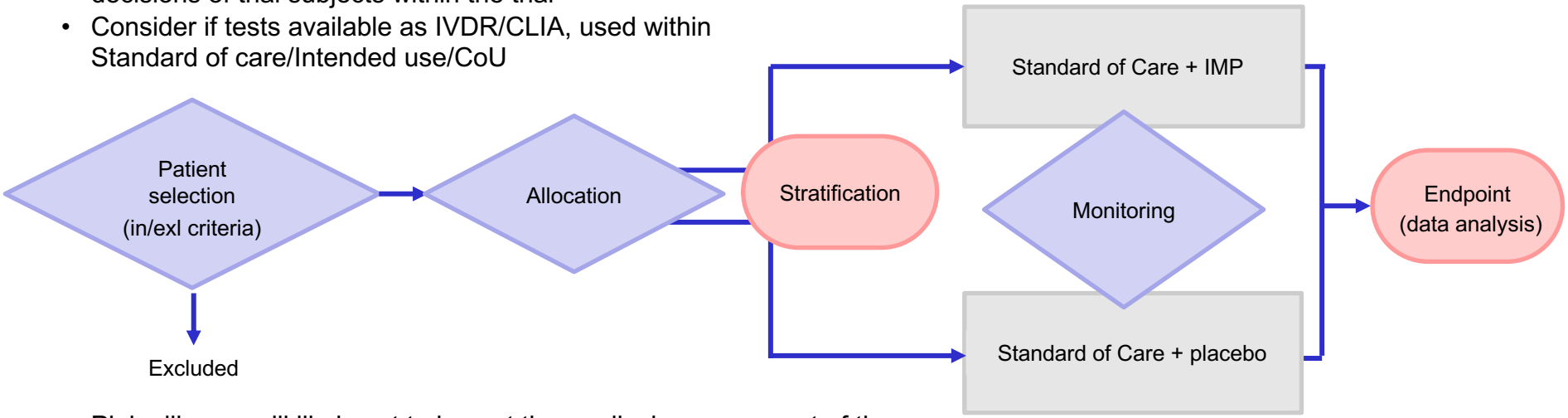
Documentation of test and Intended use

Common in US and EU	➢ Validation most often follow recommendation in CLSI guidelines • Include production and reagents, scientific validity, analytical performance and clinical performance ➢ Intended purpose/use (similar to CoU): • The use for which a device is intended according to the data supplied by the manufacturer • Is specified on the label, in the instructions for use or in promotional or sales materials or statements or as specified by the manufacturer in the performance evaluation
US	➢ Outer packaging, Inserts and Reagents shall be labelled*: ”For In Vitro Diagnostic Use"
EU	➢ Manufacturers can mark device CE (Conformité Européenne) mark on a medical device once it has passed a conformity assessment ➢ EU Member States designate accredited notified bodies to conduct conformity assessments. ➢ In some cases, the notified body must seek a scientific opinion from EMA before issuing a CE certificate – example Companion diagnostic

*Devices not represented as IVD registered shall be labelled ”For Research Use Only. Not for use in diagnostic procedures”

Consider IVDR in a clinical study? Examples

- Blue diamonds: assays which will likely be considered IVDs as they are used for medical management decisions of trial subjects within the trial
- Consider if tests available as IVDR/CLIA, used within Standard of care/Intended use/CoU

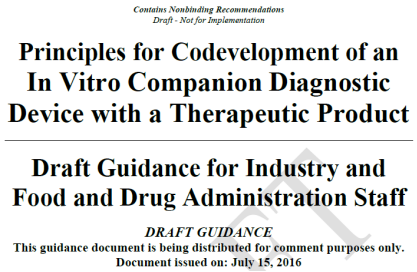


- Pink ellipses: will likely not to impact the medical management of the study subjects and with no medical purpose in the study
- Stratification assays may end up as IVDs in future clinical trials (e.g. used for allocation or monitoring) and then subject to IVDR/CLIA

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

Companion diagnostic

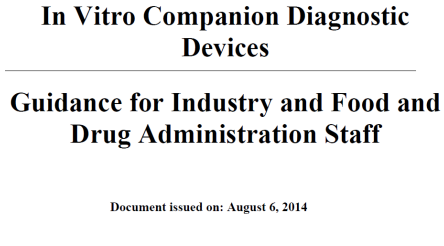
- A device that (definitions EU/EMA 2022):
  a) identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product
  b) identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product
- Different but similar requirements in US and Europe
  - US: Draft guidance present since 2011
  - Europe: IVDR registration as a co-development. Final guideline adopted in June 2022
- Validation should follow IVDR/CLIA requirements
- ”May”/”May not” be needed for tests used within Standard of care/Intended use/CoU and available as IVDR/CLIA?
- EMA and FDA recommends to interact with regulators for scientific advice


Contains Nonbinding Recommendations
Draft - Not for Implementation

Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE
This guidance document is being distributed for comment purposes only.
Document issued on: July 15, 2016


In Vitro Companion Diagnostic Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on: August 6, 2014

The draft of this document was issued on July 14, 2011.





17 June 2022
EMA/198592/2022

Guidance on the procedural aspects for the consultation to the European Medicines Agency by a notified body on companion diagnostics

Examples shared within the EBF network

- Test that may or may not be relevant of CLIA/IVDR for individual study subjects
  - Assay run at a routine diagnostic laboratory
  - Biomarker tests used for patient stratification (inclusion, safety, dose adjustment)
  - PK assay used for dose adjustment
  - Anti-AAV titers in AAV gene therapy
  - Anti-drug antibody test results for high risk project
  - Shedding assay (ie precence of gene therapy DNA/RNA in fluid, tears, semen, blood)

- Consider when individual data is necessary to share with investigators/medical doctors
- Consider if IVDR and CLIA and potentially also CDx are required
- Only report data on individual patients to investigators/medical doctors when important for project

Examples shared within the EBF network

- Test that may or may not be relevant of CLIA/IVDR for individual study subjects
  - Assay run at a routine diagnostic laboratory
  - Biomarker tests used for patient stratification (JC virus test to minimise risk for PML (progressive multifocal leukoencephalopathy) before administration of Tysabri in MS patients)
  - PK assay used for dose adjustment and safety (project ongoing at EBF member company)
  - Anti-AAV titers in AAV gene therapy (CDx for anti-AAV5 for Biomarine gene therapy Roctavian™ in severe hemophilia A, approved in EMA)
  - Anti-drug antibody test results for high risk project (eg anti-EPO)
  - Shedding assay (ie precence of gene therapy DNA/RNA in fluid, tears, semen, blood)

- Consider intended use/COU → new COU may change requirements
- Relevant for IVDR and potentially CDx → data is shared with investigators/medical doctors
- IVDR may be relevant and CDx case-by-case → if data shared with investigators/medical doctors
- Not relevant since not part of safety for individual patient → do not share individual data with investigators/medical doctors

Summary

- *In vitro* diagnostic tests are required when used with the purpose of clinical treatment, medical diagnosis, health assessment or disease prevention for a human individual

- Scientists needs to be aware of the appropriate guideline documents regarding regulatory expectations for the development of diagnostic tests
  - CLIA regulations in the US for analysis of samples from US citizens
  - IVDR regulations for products marketed in EU for analysis of samples from EU citizens

- Companions diagnostic follow the same requirements as CLIA and IVDR
  - Must be co-developed with new drug application

Acknowledgements

EBF community and EBF teams for discussion

Contact Information

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www.e-b-f.eu