From promising biomarkers to medical tests
in the era of the New EU IVD Regulation 2017/746

Prof. Dr. C.M. Cobbaert
Chair EFLM Working Group Test Evaluation
EC observer to MDCG IVD group
June 21th, 2019
Process of EU market access of medical tests under the new IVD Regulation 2017/746


Background: what exactly will change?

EU Medical Device Legislation

three Medical Device Directives

* Active Implantable MDD
  - Directives 90/385/EEC + 2007/47/EC

* Medical Devices MDD
  - Directives 90/385/EEC + 2007/47/EC

* In Vitro Diagnostic MDD
  - Directive 98/79/EC

MDR
Regulation
2017/745

IVDR
Regulation
2017/746
The purpose of MDR/IVDR legislation is to regulate the trade in medical devices and IVDs in the EU and, by doing so, to guarantee the safety, suitability and performance as well as safeguard the health and ensure the necessary protection of patients, users and other persons.
Timelines for full application

Transitional period

- 26 May 2017: Entry into force of Regulations
- 26 May 2020: Full application of MDR at 3 years
- 26 May 2022: Full application of IVDR at 5 years
IVDR key changes

I.  Scope and (Re)Classification;

II. Clinical Evidence Requirements;

III. Notified bodies and Conformity Assessment;

IV. Post-market Surveillance & Vigilance;

V.  UDI & data upload in Eudamed database;

VI. IVD-specific issues: “in house” tests
I. Scope and Classification

In Vitro Diagnostic MD

- ...any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, software or system,

- whether used alone or in combination, intended...to be used in vitro for the examination of specimens, including blood and tissue donations... from the human body,

- solely or principally for...providing information..
... solely or principally for the purpose of providing information on one or more of the following:

(a) Concerning a physiological or pathological process of 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 monitor therapeutic measures.

Companion Diagnostics
Genetic testing

SCOPE ENLARGEMENT
Including high risk "In House" tests
IVD Device Classes

- **D**
  - High public health risk
  - Blood safety / high risk infectious diseases

- **C**
  - High risk for individual patients
  - e.g. cancer markers, dangerous infectious diseases, etc.

- **B**
  - Medium risk for individual patients
  - e.g. blood chemistry, pregnancy tests, etc.

- **A**
  - Low risk for individual patients
  - Instruments, accessories, specimen collection systems etc.
NEW REQUIREMENT WITH MAJOR IMPACT!

Clinical Evidence = clinical data and performance evaluation results, pertaining to a device of sufficient amount and quality **TO ALLOW A QUALIFIED ASSESSMENT OF WHETHER THE DEVICE ACHIEVES THE INTENDED CLINICAL BENEFIT AND SAFETY, WHEN USED AS INTENDED BY THE MANUFACTURER.**
IVDR 2017/746: key change: Clinical Evidence requirement

IVD REGULATION (EU) 2017/746

Clinical Evidence Article 56
- Annex XIII Section 1.2.1: Scientific Validity
- Annex XIII Section 1.2.2: Analytical Performance
- Annex XIII Section 1.2.3: Clinical Performance

Other Evidence
- Annex I Section 10: Chemical Safety
- Annex I S. 10, 11 & 12: Biological Safety
- Annex I Section 17: Electromagnetic Compatibility
- Annex I Section 18: Mechanical Safety

Sources of Evidence
- Peer Reviewed Literature
- Consensus / Expert opinions
- Proof of concept Studies
- Performance Studies
- Information on scientific validity from devices measuring the same analyte
- Published experience gained by routine testing

Evidence Collection

Sufficient Evidence?
- YES
  - Compile Performance Evaluation Report Including Clinical Evidence (Annex XIII Section 1.3)
- NO
  - Performance Studies (Annex XIII Section 2 and Section 3)

Conformity Assessment

https://www.medtecheurope.org
Cyclical framework for the evaluation of *in vitro* medical tests

Key components of the test evaluation process are driven by the clinical need of using a test in the clinical pathway.

Horvath AR et al., CCA, 2014
IVDR Article 56

The *clinical evidence* shall be such as to scientifically demonstrate, by reference to the state of the art in medicine, that the intended clinical benefit(s) will be achieved and that the device is safe.

The *clinical evidence* derived from the performance evaluation shall provide scientifically valid assurance, that the relevant general safety and performance requirements ...are fulfilled, under normal conditions of use.
‘Reference to the state of the art’ and ‘normal conditions of use’

Clinical pathway mapping:
What is the purpose and role of the test?
Test role and purpose in the clinical pathway

Comparative accuracy: assessing new tests against existing diagnostic pathways

Patrick M Bossuyt, Les Irwig, Jonathan Craig, Paul Glasziou

Bossuyt et al. BMJ 2006
The Test Evaluation Cycle

IVDR Article 2 (40):
The ability of device to correctly detect or measure a particular analyte.

- preanalytical considerations
- analytical sensitivity/specificity
- limit of detection/quantitation
- measurement range
- linearity
- metrological traceability
- imprecision and trueness
- interferences cross-reactions

Clinical Pathway
Clinical Performance
Clinical Effectiveness
Impact
Cost
Medical Test
Biomarker
Performance
The Test Evaluation Cycle

IVDR Article 2 (41)
the ability of a device to yield results that are correlated with a particular clinical condition or a physiological or pathological process or state in accordance with the target population and intended user

- How well does it work in practice?
- In what subset of patients?
- Is it really better than Old Bore®?
- How alternative tests compare?
Health institutions should have the possibility of manufacturing, modifying and using in-house tests and thereby addressing,

✓ on a non-industrial scale,

✓ the specific needs of target patient groups

✓ which cannot be met at the appropriate level of performance by an equivalent device available on the market.

“IN HOUSE” TESTS ARE EXEMPTED!
IVDR: from a “good will” approach to “legal” Regulation

From ~85% self-declaration to ~15%;
From ~15% conformity assessment by notified bodies to ~85%.
The IVDR is vastly more “legal” in nature than its predecessor, which took more of a “good will” approach in many ways. This has **CONSEQUENCES FOR STAFFING** at CAs, NBs, EOs, Medtech Europe & IVD-manufacturers included.

The Regulation **CHANGES THE EUROPEAN REGULATORY ENVIRONMENT** as
1. more stringent clinical data requirements,
2. extended data management,
3. more complex conformity assessment procedures (particularly for high-risk tests),
4. and product liability and penalties will be introduced.

**NoBo’s are already signaling they will not be able to process all this extra work,** which may lead to compliant devices losing access to the European market.
Devices/LDTs that are manufactured or modified and used **WITHIN** health institutions shall be considered as having been put into service.

**THE REQUIREMENTS IN THE IVDR DO NOT APPLY TO LDTs PROVIDED THAT CERTAIN CONDITIONS ARE MET**, including:

- health institutions ensure that the relevant general safety and performance requirements are followed (Annex I);
- an appropriate quality management system is established;
- the health institution **justifies** that the target group’s specific needs cannot be met by an equivalent device on the market;
- information is made available to competent authorities on request;
- a declaration with certain details is made publicly available;
- reviews experience gained from clinical use of the devices and takes all necessary corrective actions.
IVDR preparations: up or out, sink or swim!

SINK
OR
swim