From Directive to Regulation: Update on the New IVDR

Gary L. Myers
Chair, JCTLM

James Pierson-Perry
Corporate Representative to IFCC Scientific Division

Graham Beastall
Chair, JCTLM WG on Traceability: Education and Promotion

**Essential Requirement of the IVD Directive**

"The traceability of values assigned to calibrators and/or control materials must be assured through available reference measurement procedures and/or available reference materials of a higher order."  

**Joint Committee for Traceability in Laboratory Medicine**

In 2002, the JCTLM was formed bringing together the sciences of metrology, laboratory medicine and laboratory quality management to help the IVD industry meet traceability requirements of the EC IVD Directive.  

*Accurate results for patient care*
JCTLM Database

- JCTLM through BIPM developed and maintains a database of Reference Measurement Systems @ http://www.bipm.org/jctlm/

- JCTLM coordinates the nomination and review process for database entries for compliance with appropriate ISO Standards

How is the IVDD changing?

In-Vitro Diagnostic Directive 98/79/EC is repealed

In-Vitro Diagnostic Regulation 2017/746/EU
In this context what is the difference between a Directive and a Regulation?

**EU Directive:**
- Applicable to all Member States
- Sets certain aims, requirements and concrete results that must be achieved in every Member State
- Member States have to adapt their laws to meet these goals, but are free to decide how to do so.

**EU Regulation:**
- The most direct form of EU law
- Immediately applicable and enforceable in all Member States
- Member States ensure their national law does not define the subject matter any further (no room for different interpretations by member states).
Transition from the IVDD to the new IVDR

- IVDR Published: May 5, 2017
- Entry Into Force: May 5, 2017
- 5 Year Transition: MFRs can meet IVDD or IVDR
- Date of Application: May 26, 2022
- Date of Full Application: May 2024
- Grace period for exiting IVDD CE: May 2024
- No CE based on IVDD may be issued

Source: bsi

The new regulation clarifies and expands the scope of regulated IVDs to include:

- Tests providing information about the pre-disposition of a medical condition or disease, for ex. genetic tests
- Tests providing information to predict treatment response to medicines, for ex. companion diagnostics
- Medical software, which is explicitly mentioned in the definition of IVDs
- Lab developed tests (LDTs) used within health institutions are also required to meet safety and performance requirements
Key Change:

- Risk Categories
  - Move from list-based approach to risk-based approach (follows GHTF rules for classification)
  - Four risk categories – A (low risk) to D (high risk)
  - New Notified Body Organizational Group (NBOG) codes for notified bodies

Key change: New risk categories of IVD devices

A (low risk) to D (high risk)

<table>
<thead>
<tr>
<th>Class A</th>
<th>Class B</th>
<th>Class C</th>
<th>Class D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low personal risk Low public health risk</td>
<td>Moderate to low personal risk, low public health risk</td>
<td>High personal risk, moderate to low public health risk</td>
<td>High personal risk, high public health risk</td>
</tr>
<tr>
<td>Accessories</td>
<td>Thyroid function</td>
<td>Syphilis (diagnosis only)</td>
<td>Hep C virus</td>
</tr>
<tr>
<td>Wash buffers</td>
<td>Clinical chemistry</td>
<td>Neonatal screening for metabolic disorders (PKU)</td>
<td>Hep B virus</td>
</tr>
<tr>
<td>Specimen receptacles</td>
<td>Self-test devices listed as not Class C</td>
<td>Pregnancy, Fertility, cholesterol tests</td>
<td>HTLV I/II</td>
</tr>
<tr>
<td>Instruments</td>
<td></td>
<td>Rubella, Cancer markers</td>
<td>Blood Grouping ABO</td>
</tr>
<tr>
<td>Culture media</td>
<td></td>
<td>Genetic tests</td>
<td>CHAGAS</td>
</tr>
</tbody>
</table>

- Syphilis (used to screen blood donations)

Source: bsi
Key Change:

- Conformity Assessment Routes
  - Amended to reflect new classification rules
  - More manufacturers will need to use a Notified Body
    ✓ Approximately 20% of IVDs are currently subject to Notified Body approval
    ✓ The number of IVDs is estimated to increase 4 fold under new IVDR

Key Change:

- Post-market Reporting and Transparency
  - Post-market performance follow-up (PMPF) new requirement
  - An electronic portal will be introduced where manufacturers can report:
    ✓ serious incidents and safety corrective actions
    ✓ field safety notices and summary reports
  - Devices must be fit with a unique device identification
Important note:

- There is no “grandfathering “ for existing products.
- All manufacturers will need to review existing products against the requirements of the regulation.
- Current devices will need to be re-evaluated and re-certified when the existing IVD Directive certificates expire.

Thank You
IVDR: IVD Manufacturers Concerns

- Effort and Cost to update and maintain Technical Files
  - No grandfathering—~85% of manufacturers’ products will require Notified Body (NB) involvement to put on market (formal submissions)
  - Many new standardized documents and requirements
  - May be difficult to find relevant data for old products—requiring new work to meet the IVDR requirements
  - Burdensome lifecycle management (some Tech Files need annual updates)
  - Estimates of £25-50K per product, then ongoing NB fees, post-commercial lifecycle management costs, etc.
  - Major drain on internal resources and competition for external consultant

- More rigorous clinical evidence is required
  - Must provide evidence of safety and performance according to a device’s assigned risk class
  - If performance data are missing, Intended Purpose will need to be limited or additional studies will need to be performed

IVDR: IVD Manufacturers Concerns

- Many literature searches required to support claims
  - Clinical performance
  - Scientific validity

- New labeling requirements
  - Lot-to-lot variation not yet defined—may impact registrations worldwide
  - No agreement yet for UDI symbol
  - Requirement to submit labeling in all lanugages to NBs where product is sold in EU

- Notified Bodies (NBs)
  - IVDR increases workload and scope to NBs
  - NBs must be designated before they can certify site or register products to IVDR
  - Many NBs not yet IVDR designated—not likely to do so until mid-2019 or later
  - No consulting services—NBs won’t answer questions or give guidance due to fear of being considered “consultants”
IVDR: IVD Manufacturers Concerns

- Agreement between Notified Bodies and EU Commission
  - Groupings not finalized for sampling of Class B and C devices
  - "Intended Purpose" has more requirements that need to be added (if not already in the IFU)—may impact registrations worldwide

- EUDAMED
  - Implementation date not yet communicated
  - Functionality of Post-Market Surveillance & Vigilance module of EUDAMED database not yet defined

- Impact of BREXIT
  - ~45% of medical devices CE marked in Europe utilize UK NBs
  - ~70% of Non-EU based manufacturers use UK NBs; e.g., Authorized Rep (AR)
  - UK-based AR will need to move or need new offices in EU country
  - Change in AR address will require updates to NB address on product labeling

IVDR: Implications for IFCC/Societies

- Education
  - Do professional organisations have a role in educating members about the IVDR?
    - If so, how should this be achieved?

- Monitoring
  - Do professional organisations have a role in monitoring and collating experience following IVDR roll out?
    - If so, how should this be achieved?

- Liaison with IVD manufacturers
  - Do professional organisations have a role in working with IVD manufacturers during IVDR roll out?
    - If so, how should this be achieved?
IVDR: Implications for IVD users

- Method status
  - Are the methods my lab uses IVDR compliant?
  - If not, when will they become IVDR compliant?

- Availability of methods
  - Will IVDR require global or just EU compliance?
  - Will IVDR limit availability of methods in EU countries?
  - Will new IVDs take longer to reach market?

- Cost
  - Will IVDR compliance increase cost of IVDs?
  - Will non-compliant IVDs be cheaper?

- Harmonisation of patient results
  - Will IVDR improve or worsen between-method agreement?