Classification & Clinical Evidence under the IVDR

Requirements of the IVDR
Proposed classification rules

- Annex II to the current IVD Directive addresses the level of risk posed by IVD medical devices by means of a positive list system.

- This system was adapted to scientific and technological development at the time the IVD Directive was written.

- Today it can no longer keep up with the fast pace of scientific and technological progress.
Proposed classification rules

- The proposed Regulation introduces a new risk-rule based classification system based on the Global Harmonization Task Force (GHTF) classification rules.

- This change to the classification system will have an impact on all manufacturers of IVDs.

- The majority of IVDs currently self-certified will now require the services of a Notified Body in the conformity assessment process to ensure the safety and performances of IVDs placed on the EU market.
Under the current IVD directive 10-15% IVD’s require Notified Body assessment.

Under the new Regulation 85-90% will require Notified Body assessment (All IVD’s except Class A - except NPT devices).
Proposed classification rules

- In the new classification system, IVDs will be divided into four classes of risk: A (lowest risk), B, C and D (highest risk)
- The conformity assessment procedure for class A devices will be carried out, as a general rule, under the sole responsibility of the manufacturer
- For devices of class B, C and D an appropriate level of involvement of a Notified Body is compulsory, proportionate to the risk class
- Devices of class D will require explicit prior approval of the design and of the quality management system before they may be placed on the market
- In the case of class B and C devices, a Notified Body is required to check the quality management system and additionally, for class C, the technical documentation of representative samples.
Proposed classification rules

Implementing rules for the classification rules

– Application of the classification rules shall be governed by the intended purpose of the devices

– If the device is intended to be used in combination with another device, the classification rules shall apply separately to each of the devices

– Accessories are classified in their own right separately from the device with which they are used

– Standalone software, which drives a device or influences the use of a device, falls automatically in the same class as the device. If standalone software is independent of any other device, it is classified in its own right.
Proposed classification rules

- Calibrators intended to be used with a device shall be classified in the same class as the device.

- Standalone control materials with quantitative or qualitative assigned values intended for one specific analyte or multiple analytes shall be classified in the same class as the device.

- The manufacturer shall take into consideration all the rules in order to establish the proper classification for the device.

- Where a device has multiple intended purposes stated by the manufacturer, which place the device into more than one class, it shall be classified in the higher class.

- If several classification rules apply to the same device the rule resulting in the higher classification shall apply.
**Rule 1**
Detection of transmissible agents in blood, tissues or organs intended for transfusion or transplantation.

Detection of a transmissible agent that causes a life-threatening disease with a high or currently undefined risk of propagation.

**Rule 2**
Reagents for blood grouping or tissue typing to ensure immunological compatibility for transfusion or transplantation.

*Except*

- Determination of ABO, Rh, Kell, Kidd, Duffy systems

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Classification & Clinical Evidence under the IVDR
Proposed classification rules

Rule 3

- Detection of sexually transmitted agents
- Detection of infectious agents with a risk of limited propagation, or where erroneous results could cause disability or death
- Pre-natal screening to determine immune status
- Selection of patients e.g. companion diagnostics
- Determination of infective disease or immune status where erroneous results could lead to a life threatening situation
- Human genetic testing
- Monitoring of medicinal products, substances or biological components where erroneous results could lead to a life threatening situation
- Management of patients suffering from a life threatening infectious disease
- Screening for congenital disorders in the foetus.

Class C
Proposed classification rules

Rule 4
Devices for self-testing

- Devices for blood gases and blood glucose determinations for near patient testing
  - Class C

Except

- Result is not for determining a medically critical status, or is preliminary and requires follow-up with a laboratory test
  - Class B

Rule 5
Reagents which possess specific characteristics to make them suitable for IVD procedures related to a specific examination
- Instruments used in IVD procedures
- Specimen receptacles
  - Class A
Proposed classification rules

Rule 6
Devices not covered elsewhere in the classification rules

Rule 7
Devices which are controls without a quantitative or qualitative assigned value.

Class B

Classification & Clinical Evidence under the IVDR
Proposed classification rules

- **Rule 1**: Blood screening
  - High risk disease

- **Rule 2**: Blood or tissue compatibility
  - Infectious disease
  - Cancer testing, Companion diagnostics, Genetic testing, TDM, Congenital screening

- **Rule 3**: High risk blood groups

- **Rule 4**: Self testing
  - High risk Near Patient Tests
  - Blood gases
  - Blood glucose NPT

- **Rule 5**: Specific IVD reagents
  - Instruments
  - Specimen receptacles

- **Rule 6**: None of the other rules

- **Rule 7**: Unassayed controls

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Classification & Clinical Evidence under the IVDR
Proposed amendments to the classification rules

- Classification shall also be governed by the novelty, complexity and inherent risk of the devices – these terms are yet to be defined

- The term embryo is now included in addition to foetus for detecting presence of an infectious agent and screening of congenital disorders

- Annex VII, section 2.3 f(ii) Class C - Devices intended for disease staging or prognosis.
Interpretation of the proposed classification rules

- IVD WG classification subgroup (from MDEG) formed to discuss classification issues

- Classification will depend upon intended use i.e., screening claims and the level of risk to the patient and the public (taking into account the likelihood of harm and the severity of that harm)

- Identical devices may be classified differently if they are to be used for different diagnostic purposes. This is why the manufacturer’s intended use of the device is critical to determining the appropriate class

- ? MEDDEV guidance to be issued as for MDD.
Issues in classifying products

- Difficulty in defining terms used in the regulation e.g., transmissable agent, does this mean that pyrogenicity tests are Class D?

- A lot of discussion amongst competent authorities regarding device classification. One CA proposed stains as Class C as screening devices for the diagnosis of cancer

- Manufacturers should classify their products under the new system to assess impact and identify any areas where the classification is unclear

- Discuss these with your Notified Body and the your Competent Authority
New Requirements for Clinical Evidence

- New Regulation gives requirements in two Annexes;
- Annex VII – Clinical Evidence and Post market follow-up
- Annex XIII - Interventional Clinical Performance Studies and other Studies involving risks for the subject
- Applies to all devices.
Clinical Evidence requirements

- The new IVD regulation introduces the term ‘Clinical Evidence’

- Manufacturers have to have a Clinical Evidence report that must contain the following:
  - Scientific validity data
  - Analytical performance data
  - Clinical performance data (if applicable)

- It should support the intended use of the IVD product

- Needs to be updated over the course of the entire product life cycle (risk analysis)
Clinical Evidence requirements

There are GHTF guidance documents that can be used;

– Clinical Performance Studies for In Vitro Diagnostic Medical devices
– Clinical Evidence for IVD Medical Devices – Key Definitions and concepts
– Clinical Evidence for IVD Medical Devices – Scientific Validity determination and Performance Evaluation
Clinical Evidence requirements

Key Definitions and Concepts

Classification & Clinical Evidence under the IVDR
Clinical Evidence requirements

Scientific Validity
Refers to the association of an analyte to a clinical condition or physiological state

Analytical Performance
Refers to the ability of an IVD to correctly detect or measure a particular analyte

Clinical Performance
Refers to its ability to yield results that relate to a particular clinical condition/physiological state for the intended use and in accordance with the target population and where applicable the intended user

For established analytes, this may be from the literature but needs to be established for novel analytes

Sensitivity/specificity, LoD, linearity, reproducibility

Data to support reference ranges etc

Classification & Clinical Evidence under the IVDR
SCIENTIFIC VALIDITY DETERMINATION

STAGE 1
Is the Scientific Validity of the analyte established?

STAGE 2
Identification of Scientific Validity information

STAGE 3
Appraisal and Analysis of Scientific Validity information

Does the information sufficiently demonstrate Scientific Validity?

YES

NO

Collect more information in support of Scientific Validity

Classification & Clinical Evidence under the IVDR
Scientific validity

- May not be required where the association of the analyte to a clinical condition or physiological state is well established
- For a new analyte or intended use, need to demonstrate scientific validity
- Can do this by:
  - Information from devices measuring the same analyte
  - Literature
  - Expert opinion
  - Results from proof of concept studies
  - Results from clinical performance studies
Performance Evaluation

Classification & Clinical Evidence under the IVDR
Performance Evaluation

Analytical performance
- Studies should always be performed, this is a requirement if interventional studies are going to be conducted
- For novel devices trueness may be difficult to demonstrate. Can use comparison to a well documented or reference method. Otherwise a clinical performance study comparing test performance to current clinical standard practice is required

Clinical performance
- The requirements are given in Section 6.1 of Annex I (diagnostic sensitivity & specificity, positive and negative predictive value, likelihood ratio)
- May not be required for established and standardised devices and for Class A devices.
Clinical Performance

- This can be demonstrated by a combination of the following;
  - Clinical performance studies
  - Literature
  - Experience gained by routine diagnostic testing

- Have to justify why clinical performance studies were not performed

- The level of detail in the clinical performance report will vary depending on the classification of the device;
  - **List B** – summary of study protocol, results and conclusions
  - **Class C** – method of data analysis, study conclusion and details of study protocol
  - **Class D** – as Class C but also including individual data points
Clinical Performance studies

– Used to demonstrate compliance with essential requirements when data is not available from other sources.

– Clinical performance study protocol should contain all relevant information concerning the study e.g.;
  – Purpose & objectives
  – Study population
  – Specimen type & collection

– Study report should be a stand-alone document, should include negative findings and be signed by a medical practitioner or other authorised responsible person.
Clinical Evidence

CLINICAL EVIDENCE – an example;

- Anti-HBs is used to determine if a patient has acquired immunity to HBsAg.

- Scientific Validity: Has the detection of Anti-HBs been associated with recovery from an HBsAg infection and as a marker of immunity?

- Analytical Performance: Are the corresponding Anti-HBs immunoassays sufficiently precise around the clinical cut-off of 10 IU/mL to reliably indicate that immunity has been acquired?
CLINICAL EVIDENCE

– Clinical Performance: Does the Anti-HBs assay detect Anti-HBs in the appropriate population i.e. those who have recovered from an HBsAg infection or to check they have acquired immunity after vaccination?

CLINICAL UTILITY:

– Can the treatment for HBsAg infection be discontinued and is it cost-effective? Can it be used to reliably measure immunity for health workers and travellers?

– Further clinical utility aspects are patient benefit, availability, health economic benefit etc.
Performance Evaluation

- Established and standardized tests. These tests:
  - have clinical guidelines or consensus for the use of the test,
  - there is more than one commercial test available, and/or international standard or reference materials exist.
  - produce comparable results for the analyte regardless of the method or the manufacturer.
  - Examples of this category include tests for liver markers (e.g. AST, ALT, bilirubin), kidney markers (e.g. creatinine, BUN), electrolytes (e.g. sodium, chloride), metabolic markers (e.g. glucose, calcium, albumin, total protein), hormones (e.g. hCG), blood gases, and biochemical tests for the identification of microorganisms.
- No clinical performance study required
Performance Evaluation

- Established and non standardized tests. These tests have:
  - clinical guidelines or consensus for the use of the test,
  - there is more than one commercial test available
  - while international reference materials may exist, results obtained from different IVD medical devices might not be used interchangeably.
- Examples of this category include tests for infectious diseases (e.g. Rubella, Hepatitis C), hormones (e.g. estradiol), cardiac markers (e.g. troponin), tumour markers (e.g. BCR-ABL, CEA, PSA), and cell markers (e.g. CD4, T-cells).
- Clinical Performance study may be required
Performance Evaluation

- Novel tests. Such tests involve:
  - a new analyte,
  - new technology,
  - new target population,
  - new application of an established technology, or
  - a new intended use, and
  - they are not established or standardized.
- Examples of this category include tests for newly identified cardiac markers (e.g. high sensitivity CRP) and tumour markers (e.g. CTC), pharmacogenomics (e.g. CCR5), emerging infectious diseases (e.g. SARS, H1N1) and other pathogens (e.g. vCJD).
- Clinical Performance Study required
Why is analytical performance often sufficient for an IVD?

Unlike medical devices, IVD test development often includes use of human specimens (‘normals’ to establish reference range and pathological samples) as part of establishing the analytical performance evaluation of a device.

The above, however, applies:
- mainly to established and standardized tests
- sometimes to established and non standardized tests
- Rarely to novel tests
Clinical Evidence

IVD Regulation relevant Annexes:

- ANNEX I – GENERAL SAFETY AND PERFORMANCE REQUIREMENTS
- ANNEX XII – CLINICAL EVIDENCE AND POST-MARKET FOLLOW-UP
- ANNEX XIII – INTERVENTIONAL CLINICAL PERFORMANCE STUDIES AND OTHER CLINICAL PERFORMANCE STUDIES INVOLVING RISKS FOR THE SUBJECTS OF THE STUDIES
Future considerations
Which IVDs are affected?

- Clinical Evidence applies in principle to all IVDs
- However, impact of Clinical Evidence will be very different for established analytes (all information will be in the literature) vs. novel analytes
- Clinical evidence requirements will be driven by risk of incorrect result, degree of innovation, novelty, degree of variability of the subject population and disease state and the intended user of the device
Summary

Clinical Performance Studies

- For e.g. innovative markers and interventional applications to demonstrate the intended use clinical performance studies are oftentimes needed.
- The requirements are similar to international IVD development and regulatory standards (FDA, SFDA).
- Authorities require submission of substantial documentation.
- No grandfathering so gap analysis required to determine if any additional work is required. For existing assays information from post market surveillance can be used.
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