The IVD Regulation
Importance for the laboratory

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IVD Directive 98

- Determines requirements for admission to EU market valid since 1998
- Conformity indicated by CE mark
- Certainly no assurance for quality
- EFLM has used the possibility to suggest improvements
- Done by former WG IVD of EFLM, now part of WG Accreditation and ISO/CEN

Suggested changes

- Risk classification of ivd's
- Traceability to highest standard possible
- Information on allowed lot to lot differences
- Easier availability of information concerning validation
- Clinical knowledge within Notified Body concerning the ivd's under evaluation
- Wide availability of in house tests and the possibility to continue
- For in house tests quality guarantee: accreditation according ISO15189

Time Line for Implementation IVD Regulation

- **25 May 2017** Valid (3 weeks after publication
- **26 May 2022** From this day on all devices which do not have a valid certificate under the Directive need to comply
- **26 May 2024** End of certificate validity. No new products can be placed on the market
- **26 May 2025** Ivd's not compliant with the Regulation can no longer be sold

Availability of products according Regulation

- Not far before 26 May 2022 and probably many not far before 26 May 2024
- Still possibility to buy product produced before 26 May for one year (Warehouse clause)
- For existing products to continue under the Regulation extra requirements have to be fulfilled
- Quite possible that manufacurers discontinue specific ivd's
- Thus contact your provider in time

Availability of products according Regulation (cont)

- Probably in the end of the allowed period
- At this moment not even possible to fulfill the requirements because new systems has to be set up (UDI, Eudamed), Notified Bodies have to be included and these have to fulfill new requirements, and extra information has to be supplied by manufacturer especially concerning clinical evaluation.
- Quite possible that products of Class A are the first ones available

Differences

- It is a Regulation , not an Directive
- Clinical Evaluation more elaborate
- Post marketing Surveillance more elaborate
- Shift to intended use instead fulfilling measurement requirements (Diabetes management versus measurement of glucose)
- For only a minority a self declaration is sufficient (Class A) and for the rest involvement of a Notified Body is required
- Notified Body has to fullfill much more specified requirements (clinical expertise)
- In house testing requires accreditation (ISO15189 or comparable) and restrictions in continuation

Regulation

- A Regulation is valid on itself in all EU countries
- It requires that National laws are in accordance
- It leads to unification in its use
- It leaves a restricted area for countries to be more strict
- In The Netherlands the activities for new Laws and national directives has started (especially because for Medical Devices the implementation date is 26 May 2020)

Classification

Annex VIII of the Regulation

- Based on the intended purpose of the ivd
- Considers safety for patient and public health
- Includes software, calibrators, control material and accessories
- Thus: Risk based

Class D

- Transmissible agents in blood and blood components
- Transmissible agents causing life-threatening diseases and have a high risk of propagation
- Determination of infectious load of life threatening diseases
- Blood group system of ABO, Rhe, K, Jk, Fy
- Examples: Hepat B, HCV, HIV, ABO/Rh

Class C

- All other blood groups and tissue typing(HLA)
- Sexually transmitted agents (SOA's)
- Infectious agents in blood and CF without risk of propagation
- Infectious agents with a serious health effect
- Prenatal investigations related to the immune system
- Immununе status for serious diseases
- Companion diagnostics
- Disease staging where result influences decision of, physician where error has serious effect

Class C (cont)

- Screening, diagnosis and staging of cancer
- Drug monitoring where an error has serious effect
- Patient management in life-threatening diseases
- Screening congenital disorders
- Devices for self-testing (excluded pregnancy, fertility, cholesterol, urine testing on glucose, leuco's and ery's)
- Devices for Near Patient Testing are classified on their own right

Class C (continued)

- Examples: tissue typing, genetic tests, companion diagnostics, glucose self-test in blood, many microbiological tests, PSA, CEA, cardiac markers, therapeutic drugs

Class A

- Products for general laboratory use, accessories with no critical function, buffer solutions, washing solutions, culture media, histological stains
- Specimenn receptables
- Instruments
- Examples: culture media, specimen receptables

Class B

- All tests which are not placed in classes A, C or D
- Examples: pregnancy self test, glucose Near Patient Test, many of the clinical chemistry and hematology standard tests

- NB: If a certain test could be placed in more than one class, the highest class will be applicable.

- The classification system will certainly lead to discussions where a Notified Body has to decide about the proposal of the manufacturer.
- Example of K mentioned in our lobbying

Requirements-Technical

Described in Annex I of the Regulation

- Comparable to Directive, but described in more detail.
- More attention for Risk Managements of producer and disclosure of residual risk
- Performance characteristics like: sensitivity, specificity, trueness, precision, accuracy, linearity, measuring range, limit of detection, cut-off, specimen collection and handling, exogeous and indogenous interferences, cross reaction and carry-over

Requirements technical (cont)

- Calibrator or control material traceable to reference material of higher metrological order
- Performance characteristics maintained during lifecycle of ivd

Requirements clinical

- Clinical performance such as : diagnostic sensitivity, diagnostic specificity, likelihood ratio, expected value in normal and affected persons
- Clinical effectiveness of ivd (Clinical Evaluation report)
- During lifecycle of product continuing evaluation in respect with literature, comparable tests of competitors, and of its clinical effectiveness

Requirements

- In fact these requirements are comparable with those desribed in ISO15189 for performing a validation and will thus apply for in house examinations
- For in house tests specifically indicated: fullfilling of requirements of Annex I

Requirements for information supplied with device

- Instruction for use
- Residual risk
- Dangerous constituents
- Lot number, storage condition, experation date, intended use (self test, NPT, but as well screening, diagnosis, etc)
- Description of calibrators and controls
- Metrological traceability of values assigned to included calibrators and control material

Requirements in documentation (cont)

- Information regarding maximum (self allowed) batch to batch variation provided with relevant figures and units of measurement
- Analytical and clinical performance characteristics
- Reference intervals
- Notice of serious incidents

Available information

- Risk class
- Design information
- Validation and verification
- Analytical performance study
- Clinical performance study
- Clinical evaluation report

Post Marketing Surveillance

Already in Directive but

- Much more explicit
- Inform user about demand for informing national authority about serious incidents
- Need of Post Marketing Surveillance Plan: how to collect this information about serious incidents, field safety corrective actions, trends, literature and complaints
- Post-Marketing-Performance-FollowUp
- Periodic Safety Update Report
- Continouos action during lifecycle

Transparancy

- Each ivd has a unique UDI (Unique Device Identifier) further divided in UDI-DI (device identifier) and UDI PI (product identifier)

- System has to be developped and set up uniformly
- Role of CAMD Competent Authority of Medical Devices
- MDCG Medical Device Coordinating Group has to be nominated

Transparancy (cont)

- All information in Eudamed (a European Data Base) which has to be filled by manufacturers, Notified Bodies, and will be accesible to patients and users.
- Eudamed will be a gigantic electronic data base which is able to receive information from many systems and is able to make it available to many users
- In my opinion it is risky. Development has started but certainly not yet in relation with availability to users

Eudamed (cont)

Eudamed contains

- Registration of devices
- UDI
- Regulation of economic operator
- Notified bodies and certificates
- Performance studies
- Vigilance and post market surveillance
- Market surveillance

In house testing

Article 5.4-6 of Regulation

- Used only in a specific health institution (HI) and not transferred to other legal entities
- Set up under ISO15189 or comparable QMS
- HI justifies no CE marked product is available with comparable level of performance
- HI provides information upon request
- For Class D rules set out in Annex VIII

In house testing (cont)

HI draws a declaration which shall be publically available and contains:

Name and address

Details about identity of ivd:

it meets general safety and performance requirements as indicated in Annex I, and indicates in which aspects it does not totally fulfill these requirements

Member states can restrict the manufacturing of these tests

In house tests (cont)

- Positiv: allowed for all classes and validated in accordance with ISO15189

- Negativ: in house test not allowed if a CE product of comparable quality is available. Will probably have as consequence that a test which has been developped by your laboratory is no longer allowed if a comparable CE product has been brought on the market,unless you acquire a CE mark

In house testing (cont)

Questions which can be expected:

- When is a test an in house test? In our opinion not if a CE marked test is slightly revised (although you need to validate and not to verify it)
- When is a CE marked test comparable to the test you developped?.

In The Netherlands we start with a sery of meetings of all stakeholders next week

Notified Bodies

Independent Certification Organisation which is designated by a national authority for assessing conformity of specified ivd's

QMS demands comparable to a Certification Body assessed by national accreditation body; need to have personnell qualified in all requirements of the IVDR concerning classification, clinical evaluation and,in principle, employed by the NoBo

Notified Bodies (cont)

Requirements in Annex VII

- Specific requirements for performance evaluation of clinical evidence
- Indicates level and duration of experience for specified functions
- Specific requirements for self tests, NPT's and companion diagnostics

- Independent consultants only allowed restrictive. Not sure what this will have as consequence because we expected that our societies could contribute in this aspect

Notified Bodies (cont)

- Notified bodies have to fullfill much more explicit requirements than under the Directive, which is strongly applauded
- Uncertainty existed concerning interpretation of specific requirements and this was one of the first activities by CAMD,the authority which is set up.
- Explicit demands are recently published. See CAMD website.

Notified Bodies (cont)

- Under the Directive less than 20% of the tests were under assessment by a notified body
- Under the Regulation more than 80-90% have to be assessd by a notified body

- This will lead to a big challenge to be ready in line with the indicated time schedule of 26 may 2024

Demands in relation with NoBo

- Class A: just declaration of producer of conformity. Must have a valid QMS and Risk Management System(RMS)
- Class B: QMS and RMS of producer assessed by NoBo; assessemnt of technical data for at least one device per class
- Class C: QMS and RMS assessed;assessment of technical data for sufficient devices per catagory

Demands in relation with NoBo (cont)

- Class D: QMS and RMS assessed; assessment of technical data for each product; has to be done for each batch. Common Specifications apply. Role of designated Reference Laboratories.

Excempt from IVDR

- Products for “research only”, but not if these have the characteristics to be used as an ivd.
- Needles
- Reference materials
- EQA material

Conclusion

- IVDR will lead to more trust in the quality of the CE mark, but is not a guarantee
- Information useful for the laboratory is easier to get: validation, allowed lot to lot difference, traceability, better post market surveillance, central information about the specific ivd (UDI) via Eudamed.
- For in house tests stricter rules, but not certain how continuation of the test will be applied.

Conclusion (cont)

- Important that the laboratories use the right on information. They need it for their accreditation according to ISO15189. It contributes to the enlightening of the efforts needed for verification instead of validation, and to obtain Measurement Uncertainty.

- Information concerning the consequences of the Regulation for the users has to be supplied in time.

Role of laboratories in the implementation process.

- In many aspects questions still exist during the implementation: in house tests, extensiveness of clinical studies to get the required evidence for already existing and new tests, possible role of experts.
- In The Netherlands a sery of meetings is set up around the implementation with all stakeholders. People involved in the central European system (CAMD) are member. This make it possible to have some influence.
- Possible role of EFLM in relation with MedTech to make the transition smooth.

Role of laboratory specialists in general: be involved

- The whole process of coming to the IVDR shows the importance to be involved as laboratory professional.
- This holds true as well in contact with the National Standard Bodies,CEN and ISO which are responsible for standards like ISO15189.
- This holds true as well for contacts with the National Accreditation Bodies, EA and ILAC in having influence concerning the way the standards are assessed.

Thanks

Questions?