Labeling of reagents (IVD, ASR, RUO, CE, FDA) and what are the consequences for you as a laboratory and for the patients

Meeting May 18, 2011

Danish Medical Devices Certification (DGM)

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Agenda

1. Who is DGM
2. The IVD Directive
   - IVD devices (and non IVD devices)
   - Essential Requirement (Annex I)
   - How to marketed a IVD device?
     - Annex II list A and B
     - (Self testing)
     - All other
3. Routes to the CE mark
4. Performance and other requirements
5. Benefits from using IVD devices

DGM

- Established in 1993 by Danish Standards, Demko A/S, Rigshospitalet, Danish Medicines Agency, Statens Serum Institut og Dansk Teknologisk Institut
- Notified in 1995 by Ministry of Health for approval of medical devices and certification according to MD Directive
- Notified in 2001 by Ministry of Health for approval and certification according to the IVD Directive
- January 2007: DS Certification was formed (owned by DS)
- DGM has approximately 10 employees

98/79/EF In-vitro Diagnostic Directive

Definition

'in vitro diagnostic medical device' means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, 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:

— concerning a physiological or pathological state, or
— concerning a congenital abnormality, or
— to determine the safety and compatibility with potential recipients, or
— to monitor therapeutic measures.

This means that e.g. alcohol tests used by the police are not IVD
This also means that Research Use Only (RUO) products and Analyte Specific Reagent (ASR) are not IVD devices

Annex I, Essential Requirements

§ A1-6 General requirements incl. risk management, manufacturing, characteristics and performance, traceability, life, transportation and storage
§ B1 Chemical and physical properties (and risks)
§ B2 Infection and microbial contamination
§ B 3 Properties on the manufacture and environments (combinations, risks, environment, waste, measuring scales and ergonomics)
§ B4 Devices which are instruments or devices with measuring function
§ B5 Radiation Protection
§ B6 Requirements for equipment which is connected as an energy source or equipped with such
§ B8 Manufacturer information

Annex I, Essential Requirements

§ B7 Requirements for devices for self testing

- **Performance**
- **Easy to use**
- **The risk of user error is eliminated**
- **Instructions For Use**

The requirements are the same for all CE marked IVD devices

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How to obtain the CE mark?

First "classification":

Devices included on Annex II:

List A:

Blood type quantification ABO-system, rhesus (C, c, D, E, e) and Kell
Markers for HIV infection (HIV 1 and HIV 2), HTLV I and II and hepatitis B, C and D

List B

Blood types anti Duffy and anti Kidd
A number of markers e.g. for rubella chlamydia, Prostate Specific Antigen (PSA), cytomegalovirus (CMV)
Devices for self testing of glucose

All other devices

e.g. pH and Blood gases, Electrolytes, WBC, HER2, EGFR, ERPR and many many more

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Annex II, List A *(e.g. blood type, HIV, hepatitis)* = NB approval

Annex V – EC type examination
- Approval of design
- Essential requirements
- Test reports
- Performance data incl. stability
- Risk analysis
- PMS
- Labeling

TYPE EXAMINATION CERTIFICATE

Annex IV
Full quality assurance
EN 13485 for the development and manufacturing process
Documentation of the essential requirements
Layman Trials Test Reports
Performance data incl. stability
Risk Analysis
Labeling
Changes approved by the NB
Systematic quality control
Methods of ensuring that the system can provide
Market Surveillance
Incident Reporting
Liability

ANNEX IV EC DECLARATION OF CONFORMITY

Annex VII
Ensuring Quality of production
- EN 13485 for the manufacturing process
- Organizational Structure
- Systematic quality control
- Methods of ensuring that the system can provide

Market Surveillance
Incident Reporting
Liability

ANNEX VII EC DECLARATION OF CONFORMITY

Batch verification

DS CERTIFICERING

CE Mark

Annex II, List B (and devices for self testing) = Approved by NB

Annex VII
Ensuring Quality of production
- EN 13485 for the manufacturing process
- Organizational Structure
- Systematic quality control
- Methods to ensuring that the system can provide

Market Surveillance
Incident Reporting
Usability

TYPE EXAMINATION CERTIFICATE

Annex V
Design Examination NB
- Approval of design
- Documentation of the essential requirements
- Layman Trials Test Reports
- Performance data incl. stability
- Risk Analysis, Market Monitor
- Labeling

ANNEX VII EC DECLARATION OF CONFORMITY

Annex IV
Full quality assurance
- EN 13485 for the development and manufacturing process
- Documentation of the essential requirements
- Layman Trials Test Reports
- Performance data incl. stability
- Risk
- Labeling
- Changes approved by the NB
- Systematic quality control
- Methods of ensuring that the system can provide
- Market Surveillance
- Incident Reporting
- Usability

ANNEX IV EC DECLARATION OF CONFORMITY

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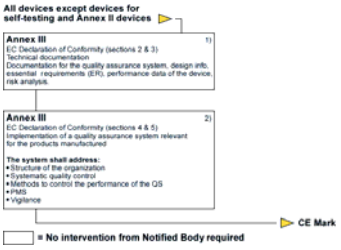
CE Mark

98/79/EF In-vitro Diagnostic Directive



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Class	IVD Directive	Standards	FDA	Canada
List A	NB: ER, QS, Batch release	ISO 13485 CTS	510(k) CLIA GMP	13485 CMDCAS HC review
List B	NB: ER, QS	ISO 13485 CTS	510(k) CLIA GMP	13485 CMDCAS HC review
All others devices	ER	CLSI	510(k) CLIA GMP	13485 CMDCAS HC review

Devices must be safe and effective

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Research Use Only (RUO) products

MEDDEV 2.14/2 rev. 1, February 2004, IVD Guidance:
Research Use Only products (and potential misuse by diagnostic laboratories).
For Research use only' products do not have an intended medical use

Consequently, when a medical purpose has been established based on sufficient and broadly agreed upon scientific, diagnostic and clinical evidence, the product must comply with the requirements of the Directive before the manufacturer can place it on the market with an intended IVD use.

Analyte Specific Reagent (ASR)

ASRs are commercially marketed products that function as building blocks for in vitro diagnostics (IVD) tests, just as active pharmaceutical ingredients are the building blocks of finished drugs and therapeutic biologics.
ASRs are used as components of laboratory-developed tests and must meet the specified criteria stated in 21 CFR 809.30.

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So what are the benefits of using CE marked IVD devices?

All devices must meet the Essential Requirements layout in Annex I of the Directive, which means it must be safe and effective.

Safe: Free from risk of: contamination, electrical shock, head burns ...

Effective: Acknowledge performance traceable to recognized standards (NIST), documented stability, interferences documented, availability of QC systems

Conclusion: Only use CE marked products

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Common Technical Specifications (2009/193/EC) - CTS
Apply from 1 December 2009 (List A and List B)
Examples:
List A: Anti-HIV-1/2 (screening):
Samples: Sensitivity: 400 HIV-1 and 100 HIV-2
Samples: Specificity: > 5000
List B: Blood Typing
For product launch: 3000 samples

The CTS includes extensive requirements for these tests

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So what are the requirements for all the other tests?

•Needs to be registered at the local Medicines Agency e.g. "Danish Medicines Agency"

•Must comply with the Essential Requirements – Annex I

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The Essential Requirements are considered meet when using harmonized to documents compliance. Below a few parameter specific standards:

CLINICAL AND LABORATORY STANDARDS INSTITUTE

H20-A2 (01/18/2007)
Reference Leukocyte (WBC) Differential Count (Proportional) and Evaluation of Instrumental Methods; Approved Standard - Second Edition

C30-A2 (08/01/2002)
Point-of-Care Blood Glucose Testing in Acute and Chronic Care Facilities; Approved Guideline - Second Edition

C46-A2 (02/24/2009)
Blood Gas and pH Analysis and Related Measurements; Approved Guideline - Second Edition

EP07-A2
Interference Testing in Clinical Chemistry; Approved Guideline - Second Edition

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Thank you for your attention

Questions?

For further information about DS Certificering A/S / DGM please refer to www.dscert.dk