Conformity Assessment of IVDs (98/79/EC)

Contents of the Presentation

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The European directive on IVD

- **Directive 98/79/EC of 27 October 1998** on IN VITRO DIAGNOSTIC MEDICAL DEVICES **("IVDDs")**
  ...came into full effect on December, 2003
  - ✓ **placing on the market**
  - ✓ **putting into service**
  - ✓ **use of IVDs**
  - ✓ **post market surveillance**

  supported by

- **COMMISSION DECISSION (2002/364/EC) of 7 May 2002** on COMMON TECHNICAL SPECIFICATIONS for *in vitro-diagnostic medical devices* **("CTS")**

- Harmonized Standards

Key Features of IVDD (I)

- All devices to be marketed in Europe have to successfully pass a Conformity Assessment acc. to the respective Directive
- Compliance to European Requirements is indicated by the CE mark on the product
- It is the **manufacturer's responsibility** to ensure conformity
- Devices must comply with **Essential Requirements (Ax I)**
- Conformity may be achieved by meeting the requirements of **Harmonized Standards**
- Performance and quality control testing must meet **CTS** whenever these are available for a product
- Compliance must be evident in the **Technical Documentation**
- Depending on the **risk** associated with the intended use of an individual device, the device is **classified**. The class of a device defines the available options/routes for **Conformity Assessment**

Key Features of IVDD (II)

- Devices of higher risk class require participation of a **Notified Body** in conformity assessment
- The manufacturer can **select** the conformity assessment route and Notified Body, if options are available
- Manufacturers outside the EU must have a **Representative in the EU**
- The manufacturer respectively his European Representative has to **register** the products at the Competent Authority of his EU member state
- Incidents, near incidents, and recalls have to be **reported** to Competent Authorities (Vigilance)
- Beside legislation **Competent Authorities** are responsible for registration, market surveillance, and designation and monitoring of Notified Bodies

Technical Documentation (IVDD Annex III, IV, and V)

= **Basis for every conformity assessment**

Central elements:

- ✓ Device description (incl. intended use, legal manufacturer, manufacturing sites)
- ✓ Prove of compliance to Essential Requirements (ER Checklist + data) incl. references to harmonized standards applied and CTS if applicable
- ✓ Risk / Benefit assessment of the manufacturer
- ✓ Qualification / performance evaluation data / stability data
- ✓ Instruction for Use / Labeling
- ✓ Description of the manufacturing process incl. QC activities
- ✓ Material-, manufacturing-, and release specifications
- ✓ Declaration of Conformity

➢ **see NB-MED/2.5.1/Rec 5 for details regarding compilation**

Classification acc. to IVDD (I)

IVD is each medical product that is

- reagent
- reactive product
- calibration material
- control material
- kit
- instrument
- device, or a system

and that shall be used for the <u>in vitro investigation</u> of specimens originating from the human body (*saliva, perspiration, excrements, blood, tissue samples*), to provide information

- concerning a physiological or pathological state
- concerning a congenital (inherited) abnormality
- to determine the safety and compatibility with potential recipients
- to monitor therapeutic processes

Specimen receptacles (for in-vitro samples storage) are IVDs.

Classification acc. to IVDD (II)

In-Vitro Directive relates to medical devices for in vitro diagnostics and their accessories.

Excluded are:

- products for general laboratory use, provided that the manufacturer did not appointed those products as specialised for in-vitro testing
- invasive sampling devices for collecting samples for in-vitro diagnostic
- IVD devices produced and used in the same institution, without any transport or sale to other bodies

Classification acc. to IVDD (III)

The directive recognises four categories of IVD depending on the risk which they present to the user:

- ✓ General IVDs
- ✓ IVDs for self-testing, i.e. test kits used in a home environment (excluding self test devices covered by Annex II)
- ✓ IVDs in Annex II, List B of the Directive, e.g. test kits for Rubella, Chlamydia, CMV, PSA, or the major tissue typing groups
- ✓ IVDs in Annex II List A of the Directive, e.g. test kits for HIV, hepatitis B, C, or D, HTLV and the major blood groups

Classification acc. to IVDD (IV)

- Classification of IVD products is performed acc. to **List A** and **B** of **Annex II** of the Directive and used for **self-testing**
- Criteria for listing devices in list A and list B are associated with:
  - risk in blood transfusion / transplantation
  - prevention of AIDS and certain types of hepatitis
  - protection for newborns
  - minimizing long term damages due to certain illnesses
- All devices listed in Annex II and intended for self-testing require participation of a Notified Body in Conformity Assessment
- All other IVD products do not require a Conformity Assessment under participation of a Notified Body

Annex II, list A of IVDD

- reagents, related calibrators and control materials, for determining the following blood groups:
  - ABO system
  - rhesus system (C, c, D, E, e)
  - anti-Kell
- reagents, related calibrators and control materials, for the detection, confirmation and quantification in human specimens of markers of
  - HIV infection (HIV 1 & 2) Human Immunodeficiency Virus
  - HTLV I and II (Human T-cell Lymphotropic Virus)
  - and hepatitis B, C and D

Blood grouping products covered by Annex II

Products:

Reagents, reagent products, calibrators, and controls for determination

List A:

- ABO-System
- Rhesus (C, c, D, E, e)
- anti-Kell

List B:

- anti-Duffy
- anti-Kidd
- irregular anti-erythrocyte antibodies

Blood grouping products NOT covered by Annex II

IVDs for self-testing:

- none

Other IVD products:

- other blood group systems / antigens (N, M, S, Le, C^{wk}, etc.)
- sample containers / stabilization / transport systems
- sample preparation systems, i.e. nucleic acid extraction systems
- specific instruments and software

Annex II, list B of IVDD

- IVD for determining the following blood groups: anti-Duffy & anti-Kidd
- IVD for determining irregular anti-erythrocytic antibodies
- IVD for the detection of the congenital infections: rubella, toxoplasmosis
- IVD for diagnosing of phenylketonuria
- IVD for determining infections by cytomegalovirus, chlamydia
- IVD for determining the HLA tissue groups: DR, A, B
- IVD for detection tumoral marker: PSA
- IVD for evaluating the risk of trisomy 21
- IVD for self-diagnosis of blood sugar content

Registration (IVDD Art. 10)

at the Competent Authorities of the Member State of his registered place of business (of authorized representative)

and – *as long as no European databank is available* – to the competent authorities of all member states where the product is placed on the market:

- Address of registered place of business
- Information on the products (indications, characteristics), significant changes, discontinuation
- For Annex II and self-testing devices data allowing identification, label, IFU, and certificates of Notified Body and any change thereto
- For Annex II and self-testing devices member states may request data allowing identification, label, and IFU when products are placed on their markets
- New products have to be indicated when registered

Vigilance Procedure in IVDs

- IVD products are as well as other medical devices a subject of vigilance procedure (the essential requirement of the administrative type)
- The manufacturer shall have a procedure for post market surveillance and reporting of adverse incidents.
- The documentation system should be established, where any positive, but especially negative information from users, physicians and another person or bodies are collected and archived.
- Acquired information shall the manufacturer immediately send to national authority, responsible for the vigilance

Prerequisites for Conformity

1) **Adequate Design** of a Device

2) **Consistent Reproduction** of the Device as designed

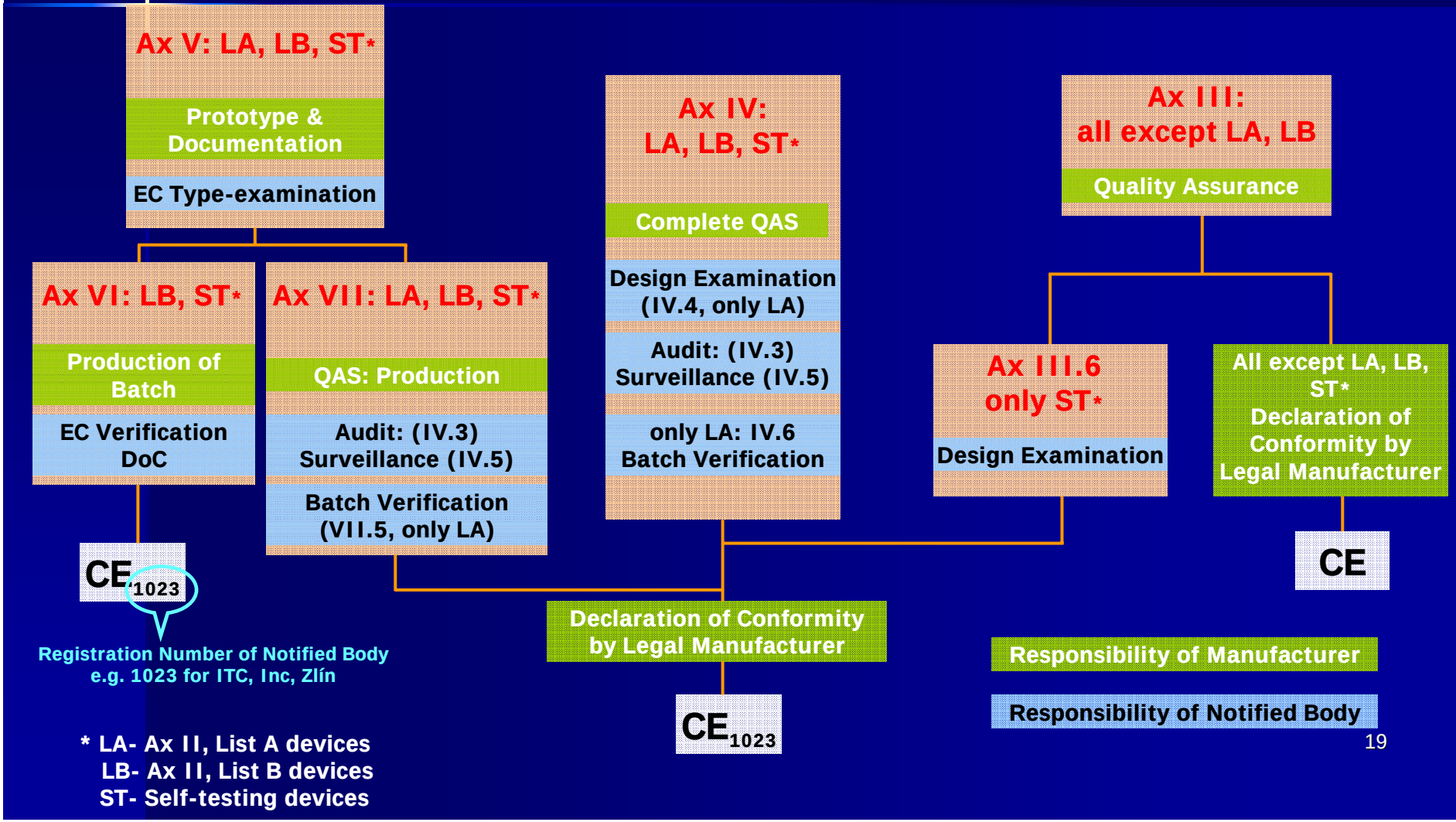
3) **Adequate Verification** of the Quality of the Device

Conformity assessment procedures IVDD

Modules used:

- Design Evaluation
  - Design Examination (Annex IV.4) – Document Review
  - Type Examination (Annex V) – Prototype Testing
  - Design Examination (Annex III.6) – Document review
- Assessment of Implementation of Quality Management System Requirements (initial and annual recurring)
  - with Design Process incl. Technical File Review (Annex IV.3)
  - without Design Process (Annex VII.3)
- Testing of Manufactured Products
  - EC Verification (Annex VI)
  - Batch Verification (Annex IV.6 & VII.5)

Conformity assessment procedures IVDD



* LA- Ax II, List A devices
LB- Ax II, List B devices
ST- Self-testing devices

Conformity assessment procedures IVDD

For List A devices, Manufacturers can choose between two routes:

Route 1 – Full Quality Assurance System

consisting of

- Design Dossier review (IV.4) = **Document Review**
- Certification & Surveillance Audits (IV.3 / IV.5)
- Verification of every batch (IV.6)

OR

Route 2 – EC Type-Examination + Production Quality Assurance

consisting of

- EC Type-Examination/Testing (V) = **Physical Testing**
- Certification & Surveillance Audits (VII.3 / VII.4)
- Verification of every batch (VII.5)

Conformity assessment procedures IVDD

For List B devices, a third is possible (optional to Route 1 or 2):
Route 3 – EC Type Testing + EC Verification
consisting of

- EC Type-Examination (V) = **Physical Testing**
- EC Verification (VI) = **Physical Testing** of every device or via strategic sampling

For Self-testing devices, another route is possible (optional to Route 1 to 3):
Route 4 – Design Examination (III.6) = **Documentation Review**

Design Dossier / Technical File Evaluation

- ✓ intended use
- ✓ specifications
- ✓ ER Checklist with reference to utilized harmonized standards
- ✓ risk analysis
- ✓ chemical & biological safety
- ✓ suitability of packing
- ✓ qualification / **performance evaluation** data of the device
- ✓ stability data
- ✓ labeling, instruction for use
- ✓ manufacturing process
- ✓ QC-testing regimen and acceptance criteria
- ✓ draft of Declaration of Conformity

Performance Evaluation acc. to IVDD

Performance evaluation data

- ✓ are necessary for **all** devices
- ✓ performance data should originate from studies in clinical or other appropriate environment and / or results from relevant biographical references
- ✓ performance to be shown in comparison with CE marked reference tests
- ✓ Annex VIII of IVDD describes requirements for devices to be used in performance evaluation and respective procedure

- ✓ Art. 5 establishes the requirement for Annex II List A devices to meet **Common Technical Specifications**:
  - performance evaluation and re-evaluation criteria
  - batch release criteria
  - reference methods & reference materials

The CTS Structure

1. Scope
2. Definitions
3. Common Technical Specifications (CTS) for products defined in Ax II List A

3.1 CTS for performance evaluation of reagents & reagent products for the detection, confirmation and quantification in human specimens of markers of HIV infection (HIV 1 & 2), HTLV I and II, and hep B, C, D. General Principles .....

3.2 Additional requirements for Nucleic Acid Amplification Techniques (NAT)

3.3 CTS for the manufacturer's release testing of reagents and reagent products for the detection, confirmation and quantification in human specimens of markers of HIV infection (HIV 1 & 2), HTLV I & II, and hepatitis B, C, D (Immunological assays only)

3.4 CTS for performance evaluation of reagents & reagent products for determining the blood group antigens: ABO system (A,B), rhesus (C, c, D, E, e) and Kell

3.5 CTS for the manufacturer's release testing of reagents and reagent products for determining the blood group antigens: ABO system (A,B), rhesus (C, c, D, E, e) and Kell

The CTS - Tables

Table 1: ”Screening” assays: anti HIV 1 & 2, anti HTLV I & II, anti HCV, HBsAg, anti HBc”

Table 2: Nucleic acid amplification techniques (NAT) for HIV 1, HCV, HBV,HTLV I & II (qualitative and quantitative tests)

Table 3: Rapid tests: anti HIV 1 & 2, anti HCV, HBsAg, anti HBc, anti HTLV I & II

Table 4: Confirmatory / supplementary assays for anti HIV 1 & 2, anti HTLV I & II, anti HCV, HbsAg

Table 5: HIV1 antigen

Table 6: Serotyping assay: HCV

Table 7: HBV markers: anti HBs, anti HBcIgM, anti HBe, HBeAg

Table 8: HDV markers: anti HDV, anti HDV IgM, Delta Antigen

Table 9: Blood Groups ABO, rhesus (C,c,D,E,e), and Kell

Table 10: Batch release criteria for Blood Groups ABO, rhesus (C,c,D,E,e), and Kell

Items / Function inspected during audits

EN ISO 13485:2003 applies for IVD

- QM-Documentation
- Management Responsibility
- Design process
  - Performance Evaluations
  - Change Control
- Technical Documentation
- Production
  - Instructions, Records, Conditions, Traceability
  - Packaging, Labeling
  - Process validation, Equipment Validation, Software Validation
- Storage, Transport
- Quality Control
- Maintenance, Calibration
- Human Resources, Training
- Purchasing, Supplier Contracts
- Marketing activities
- Customer Service
  - Complaint Handling
- Regulatory Affairs
  - Classification of products
  - Vigilance system / issues
- Quality Assurance
  - CAPAs
  - Internal Audits

Batch Verification of IVDs (List A)

Objective and Measures

- Ensuring of batch to batch consistency by monitoring
- Consideration of test results obtained by manufacturer and independent test laboratory
- Values obtained must be within a predefined range

Generally accepted test results from:

- IVD –Testing Laboratory at Paul-Ehrlich-Institut (PEI), Langen

Obligations of the Manufacturers

The manufacturer has the following obligations to NB:

- Notification of all significant changes in the quality management system, production technology and product portfolio
- Notification of all significant changes to the design and manufacture of Annex II List A products
- Notification of all reportable incidents or near incidents for products under the scope of the EC certificate
- For Annex II List A products: Provision of all batches for verification of manufactured product before release to market
- To allow annual audits and - in case of problems - ad hoc audits by the Notified Body at related facilities.

Important Harmonized Standards for IVD (I)

For a current list of harmonized standards see:
http://ec.europa.eu/enterprise/newapproach/standardization/harmstds/reflist/invimedd.html

Selected Standards

- EN 375:2001 *Information supplied by the manufacturer with in vitro diagnostic reagents for professional use*
- EN 980/A2:2001 *Graphical symbols for use in the labeling of medical devices*
- EN 12286:2000 *In vitro diagnostic medical devices -Measurement of quantities in samples of biological origin -Presentation of reference measurement procedures*
- EN 12287:1999 *In vitro diagnostic medical devices - Measurement of quantities in samples of biological origin - Description of reference materials*

Important Harmonized Standards for IVD (II)

- EN 13612:2002 *Performance evaluation of in vitro diagnostic medical devices*
- EN 13640:2002 *Stability testing of in vitro diagnostic medical devices*
- EN 13641:2002 *Elimination or reduction of risk of infection related to in vitro diagnostic medical devices*
- EN 13975:2003 *Sampling procedures used for acceptance testing of in vitro diagnostic medical devices. Statistical aspects*
- EN ISO 14971:2000 *Medical devices -Application of risk management to medical devices*
- EN ISO 17511:2003 *In vitro diagnostic medical devices - Measurements of quantities in samples of biological origin - Metrological traceability of values assigned to calibrators and control materials*

Important Harmonized Standards for IVD (III)

- EN 591:2001 *Instructions for use for in vitro diagnostic instruments for professional use*
- EN 61010-2-101:2002 *Safety requirements for electrical equipment for measurement, control and laboratory use -Particular requirements for in vitro diagnostic (IVD) medical equipment (General requirements see EN 61010-1 : 2001)*

Thank you for attention

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