CE Marking for IVD (In-vitro Diagnostic Device)

Medical device can be categorized as medical device, IVDD (In-vitro diagnostic medical device) and AIMD (Active implantable medical device). In case of CE, medical device and in-vitro diagnostic device are definitely categorized. Nowadays, medical device manufacturer is interested in developing high technology medical device (ex: medical device with medicine, combination medical device) and manufacturing in-vitro diagnostic device. I would like to inform you about CAP (Conformity Assessment Procedure) of IVDD (In-vitro diagnostic medical device) because CE Marking procedures are common CAP (conformity assessment procedure) of medical device in the world.

1. Definition of Terms
   1) In-vitro Diagnostic medical device

   You can check following definition in Directive 98/79/EC.

   (b) ‘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

   Specimen receptacles are considered to be in vitro diagnostic medical devices. ‘Specimen receptacles’ are those devices, whether vacuum-type or not, specifically intended by their manufacturers for the primary containment and preservation of specimens derived from the human body for the purpose of in vitro diagnostic examination.

   Products for general laboratory use are not in vitro diagnostic medical devices unless such products, in view of their characteristics, are specifically intended by their manufacturer to be used for in vitro diagnostic examination;

   2) Device for self-testing

   (d) ‘device for self-testing’ means any device intended by the manufacturer to be able to be used by lay persons in a home environment;
2. Classification and CAP of IVDD

1) Classification

Classification of IVDD is divided by 4 classes according to risk. It follows Annex II in Directive 98/79/EC.
- General
- Self-testing (except for device for self-testing belonging to Annex II)
- List B Ex) Diagnostic Kit of rubella, toxoplasmosis or tumoral marker: PSA etc.
- List A Ex) Reagents and reagent products, including related calibrators and control materials, for determining the following blood groups: ABO system, rhesus (C, c, D, E, e) anti-Kell,

* All IVDDs belong to General class except for List A and B in the Annex II. If some general class IVDD is intended for self-testing, they belong to self-testing class. General class IVDDs are lowest hazard class and List A class IVDDs are highest hazard class.

2) Conformity Assessment Procedure according to classification

- Conformity Assessment Procedure of List A
  * 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)

* 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 Procedure of List B
  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

- Conformity Assessment Procedure of Self-Testing
  another route is possible
  (optional to Route 1 to 3)
* Route 4 - Design Examination (III.6) = Documentation Review

- Conformity Assessment Procedure of General
  It is similar with Medical device Class I

3. Performance evaluation of IVDD according to Directive 98/79/EC

- 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

- Refer to Standard EN 13612: 2002 about general performance evaluation
- CTS (Common Technical Specification), document announced from European Union, is standard of test about List A IVDDS.

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 HBdGm, 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

4. Audit

The audit of IVDDs is based on Standard ISO 13485:2003. When IVDDs are audited, auditors audit following:

- 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
- Storage, Transport
5. Conclusion

Classification of IVDDs is simpler than general medical device and CAP of IVDDs is similar with CAP of medical device.

To acquire CE Mark of IVDDs, manufacturer should consider the performance evaluation and to prove performance evaluation, manufacturer should prepare test results according to logical and reasonable test procedure. Performance evaluation data is necessary in the TCF (Technical Construction File).

* You can find harmonized standards about IVD following site.