IVD-Directive Working Group

reports to Quality and Regulations Committee

(Committee Chair: Wim Huisman, NL)

WG Start date: Jan 2014

Chair: Christos Kroupis (GR)

Full Members: Marc Thelen (NL)

Javier Gella (ES)

Ilenia Infusino (IT)

Corresponding Members: Bernard Gouget (FR), Nuthar Jassam (UK), Maria Lohmander (SE), Marit Sverresdotter Sylte (NO)

EDMA Representatives: Alain Gamblin (STAGO)

Oswald Sonntag (BIORAD)

In close collaboration with Accreditation and ISO/CEN standards-WG (WG Chair: Michel Vaubourdolle, FR)

EFCC IVD-Working Group
reported to Quality Management Committee
Start date: April 2010

Chair: *Prof. Jean-Claude Libeer (BL)*
Full Members:
Marc Thelen (NL)
Jean-Claude Giroud [(FR) – EDMA (Biorad)]
Corresponding Members:
Christos Kroupis (GR)
Vladimir Antonov (RU)

In close collaboration with ISO/Accreditation-WG
*(**Chair:** Wim Huisman, NL)*

Equipment Maintenance guidelines

❖**Installation**

Certificate that meets specification (not only EMC compatibility)

❖**Repairs**

Documentation of all repairs and all replaced or modified parts (+software) – Lab approval/validation before equipment use

❖**Preventive maintenance report**

Documentation of all measeruments (and allowed specifications)
Traceability
Pass/fail: final conclusion

❖**Software modifications και updates**

Documentation – Lab approval

In accordance with ISO 15189

Common statement from the EFCC and EDMA on laboratory tests, offered via internet

EFCC connects National Societies of Clinical Chemistry and Laboratory Medicine and creates a platform for all specialists working in the field in Europe. EFCC provides European leadership in clinical chemistry and laboratory medicine to national professional societies, to diagnostic industry and to governmental and non-governmental organisations in order to serve the public interest in health care. For more information, please visit the EFCC website

EDMA, the European Diagnostic Manufacturers Association, represents national associations and major companies engaged in the research, development, manufacture or distribution of *In Vitro* Diagnostic (IVD) tests in Europe. More information is available on the EDMA website.

A large variety of laboratory tests are currently offered via the worldwide web (Direct-to-consumer testing).

-Qualification of these laboratories is widely different. For a quality guarantee, laboratories offering tests through internet should at least be accredited to the worldwide accepted standard for medical laboratories ISO 15189.
-Laboratory tests give information on diagnosis, follow-up of therapy, treatment and prognosis in a given particular clinical context. A standing alone lab result does often not allow to make conclusions for a particular patient.
-Interpretation of test results must be done by trained and educated people (or professionals/specialists). Therefore they need additional information on the patient for those the tests is requested. This information will be obtained from questioning of the patient, from other laboratory test results and from other clinical examinations.
-We advice people who wants to use this service to be careful on false expectations and wrong information on some websites. Often you will not have the information you really expect. All information available on the internet is not trustable. A non-commercial online portal that provides information to patients on laboratory tests that are used for the diagnosis and treatment of diseases is "Lab tests online" (www.labtestsonline.info) available in many languages.
-No well managed transport conditions (real danger on long distance transports) can affect the validity of laboratory test results and clinical utility derived.
-In many cases internet offered tests are more expensive than tests prescribed by your own physician after a clinical examination and reimbursed by the social security system in many countries.
-Access to your personal data might not be 100% safe!

CE-IVD reagent inserts

directive 98/79 EC, items of annex1, 8 Method/parameter	Glu	Urea	Crea
kit insert and date of issue of last revision	ok	ok	ok
changes in the kit insert	no change alerts	no change alerts	no change alerts
storage conditions, unopened; opened	ok	ok	ok
type of appropriate sampling tubes	no mention about gel barriers effect	no mention about gel barriers effect	no mention about gel barriers effect
principle of the method-References	ok	ok	ok (picrates)
analytical sensitivity	ok	ok	ok
diagnostic sensitivity	no data	no data	no data
analytical specificity	no	no	no
diagnostic specificity	no data	no data	no data
accuracy	no data	no data	no data
repeatability	at one level, serum sample	at one level, serum sample	at one level, serum sample
reproducibility	at one level, serum sample	at one level, serum sample	at one level, serum sample
interferences- Limitations	ok	ok	ok
limits of detection-quantitation	ok	ok	ok
Linearity-measurement range	ok	ok	ok
traceability of values assigned to calibrators	no available reference material	no available reference material	none with available reference material BCR-573/5
information on internal quality control	ok	ok	ok
information on specific validation procedures	no	no	no
reference intervals	ok	ok	ok
description of the appropriate reference population	no	no	no
intended use	ok	ok	ok
comparison with reference method	no, only between different analyzers of the same company	no, only between different analyzers of the same company	no, only between different analyzers of the same company

WG Terms of Reference (ToR)

- **Interpretation and harmonization of the use of the EU IVD Directive in laboratory practice and during accreditation of laboratories in Europe**

- **Improvement of information given by IVD manufacturers to their customers (laboratories)**

- **Guidance and recommendations for laboratories, vendors or distributors of IVD equipment and assessors on the requirements for the documentation (needed in the scope of accreditation) for the documentation of installation and preventive maintenance of equipment**

- **Guidelines for method validation/verification reports in different fields of laboratory medicine**

- **Influencing the EU regulatory frameworks related to IVDs**

IVD 98/79/EC directive

-Harmonized Standards

CEN/TC 140 *In vitro diagnostic medical devices*

ISO/TC 212 *Clinical laboratory testing and in vitro diagnostic test systems*

-Legal representative

-Essential principles

-Declaration of conformity

-Notified Bodies (after IVD reagent introduction into market! – no common acceptance criteria –no common EU oversight committee)

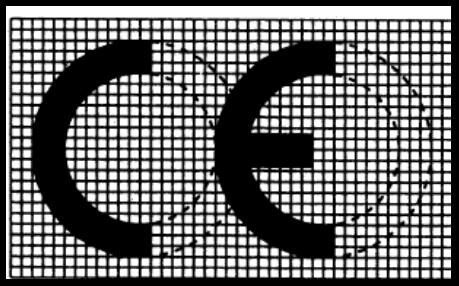
-Vigilance

-Only in parameters of a Positive list increased demands for use validation and increased production statistical control:

List B (HLA A/B/DR, TORCH, trisomy 21, PSA, PKU, POCT Glu)

List A (ABO, rhesus, HIV1/2, HTLV I/II, HBV, HCV, HDV)

CE Marking



Reference of directive/regulation	Subject of directive/regulation
2000/9/EC	Cableway installations
(EC) 1907/2006	Chemical substances (REACH)
89/106/EEC	Construction products (CPD)
(EU) 305/2011	Construction products (CPR)
(EC) 1223/2009	Cosmetics
92/42/EEC	Ecodesign – hot-water boilers
2010/30/EU	Ecodesign and energy labelling
2009/125/EC	Ecodesign and energy labelling
(EC) 1221/2009	Eco-management and audit scheme (EMAS)
2004/108/EC	Electromagnetic compatability (EMC)
94/9/EC	Equipment for explosive atmospheres (ATEX)
93/15/EEC	Explosives for civil uses
2009/142/EC	Gas appliances (GAD)
95/16/EC	Lifts
2006/95/EC	Low Voltage (LVD)
2006/42/EC	Machinery (MD)
2004/22/EC	Measuring instruments (MID)
93/42/EEC	Medical devices (MDD)
90/385/EEC	Medical devices: active implantable
98/79/EC	**Medical devices: in vitro diagnostic (IVDs)**
(EC) 765/2008	New legislative framework (NLF)
2009/23/EC	Non-automatic weighing instruments (NAWI)
94/62/EC	Packaging and packaging waste
89/686/EEC	Personal protective equipment (PPE)
97/23/EC	Pressure equipment (PED)
2007/23/EC	Pyrotechnic articles
1999/5/EC	Radio and telecommunications terminal equipment (RTTE)
2008/57/EC	Rail system: interoperability
94/25/EC	Recreational craft
2011/65/EU	Restriction of the use of certain hazardous substances (RoHS)
2009/105/EC	Simple Pressure Vessels
2009/48/EC	Toys safety

http://www.newapproach.org/Directives/DirectiveList.asp

Clinical Laboratory Improvement Amendments (CLIA) for clinical labs in USA (1988, rev2003)

Centers for Medicare & Medicaid Services (CMS) +FDA +CDC

Testing categories:

-Waived Complexity

-Moderate Complexity

+Provider-Performed Microscopy Procedures (PPMP)

-High Complexity

Lab Certificates:

Certificate of Waiver (CW)

Certificate for Provider-Performed Microscopy Procedures (PPMP)

[Certificate of Registration (COR)]

Certificate of Compliance (COC)

Certificate of Accreditation (COA)

} *for moderate/high complexity tests*

Accreditation bodies: JC, COLA, CAP

http://www.cms.hhs.gov/clia/

Reagent classification according to FDA (USA):

IVDs:

-Cleared/notification 510(k) [~2.000 $]

-Approved (pre-market approval, PMA) [~50.000 $]

ASRs (analyte specific reagents):

Class I: most (exempt), Class II (510k), Class III (PMA with GMP)

ASRs sold to:

-manufacturers

-CLIA accredited clinical labs for high complexity LDTs (with disclaimer: non-FDA cleared or approved test)

-research/other use

RUO (Research use only):

-Not regulated by FDA, illegal to bill Medicare for such research tests, disclaimer needed: not for use in diagnostic procedures

-Only allowed for LDTs & accredited labs when IVDs or ASRs are not available

IUO (Investigational use only):

for performance evaluation only of IVDs. Needs:

-informed consent from patients + disclaimer

-institutional review board (IRB) approval

-investigational device exemption (IDE) approval by FDA

Goal of the IVD directive revision

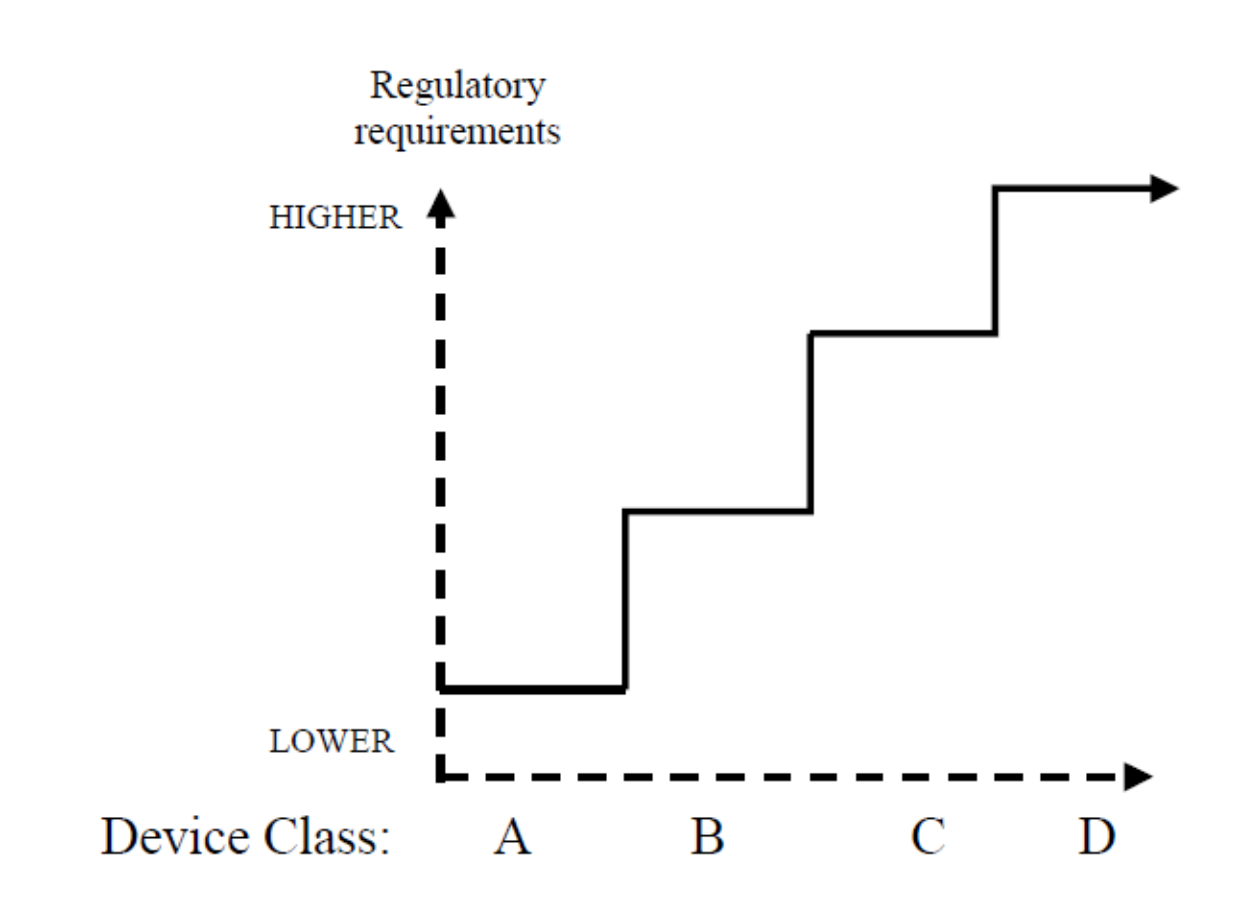
Coalescence in:

A) the views of the public for increased safety
B) the views of the manufacturers for rational cost so that they continue to produce and offer reagents in the European integrated market
Γ) and support motivation in product improvements, investing in novel technologies and finding solutions in rare diseases

Over-regulation?
Australian example: 1% global IVD market

Favoloro E.J. et al., CCLM (2011), 49, 1965-73

New rules-based classification GHTF (Global HarmonizationTask Force)



Proportional model

http://www.ghtf.org/

5 founding members: EU, USA, Canada, Australia, Japan

+ Brazil, WHO (observer) →International Medical Device Regulators Forum

GHTF proposal for classification and Conformity assessment

CLASS	RISK LEVEL	EXAMPLES
A	Low Individual Risk and Low Public Health Risk	Clinical Chemistry Analyser , prepared selective culture media
B	Moderate Individual Risk and/or Low Public Health Risk	Vitamin B12, Pregnancy self testing, Anti-Nuclear Antibody, Urine test strips
C	High Individual Risk and/or Moderate Public Health Risk	Blood glucose self testing, HLA typing, PSA screening, Rubella
D	High Individual Risk and High Public Health Risk	HIV Blood donor screening, HIV Blood diagnostic

Positive list

→ **List B**

(HLA A/B/DR, TORCH, PKU, trisomy 21, PSA, POCT Glu)

→ **List A**

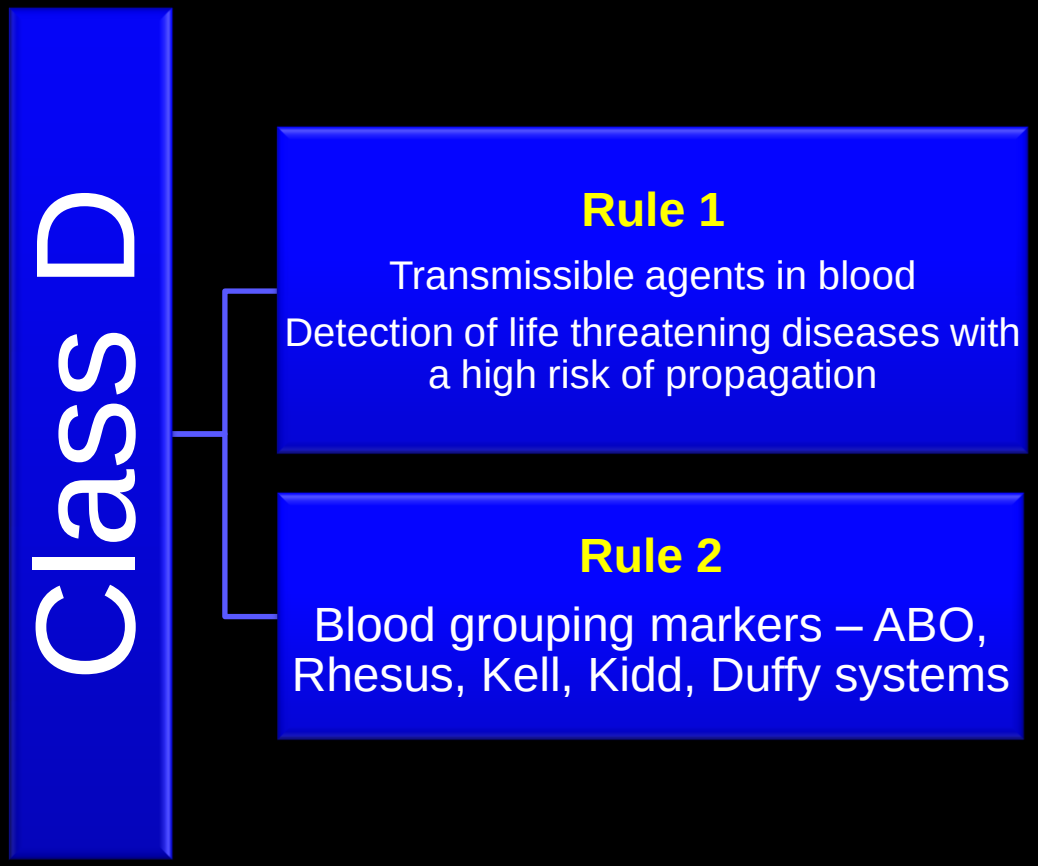
(ABO, rhesus, HIV1/2, HTLV I/II, HBV, HCV, HDV)

+ genetic tests, flow cytometry, theranostics etc

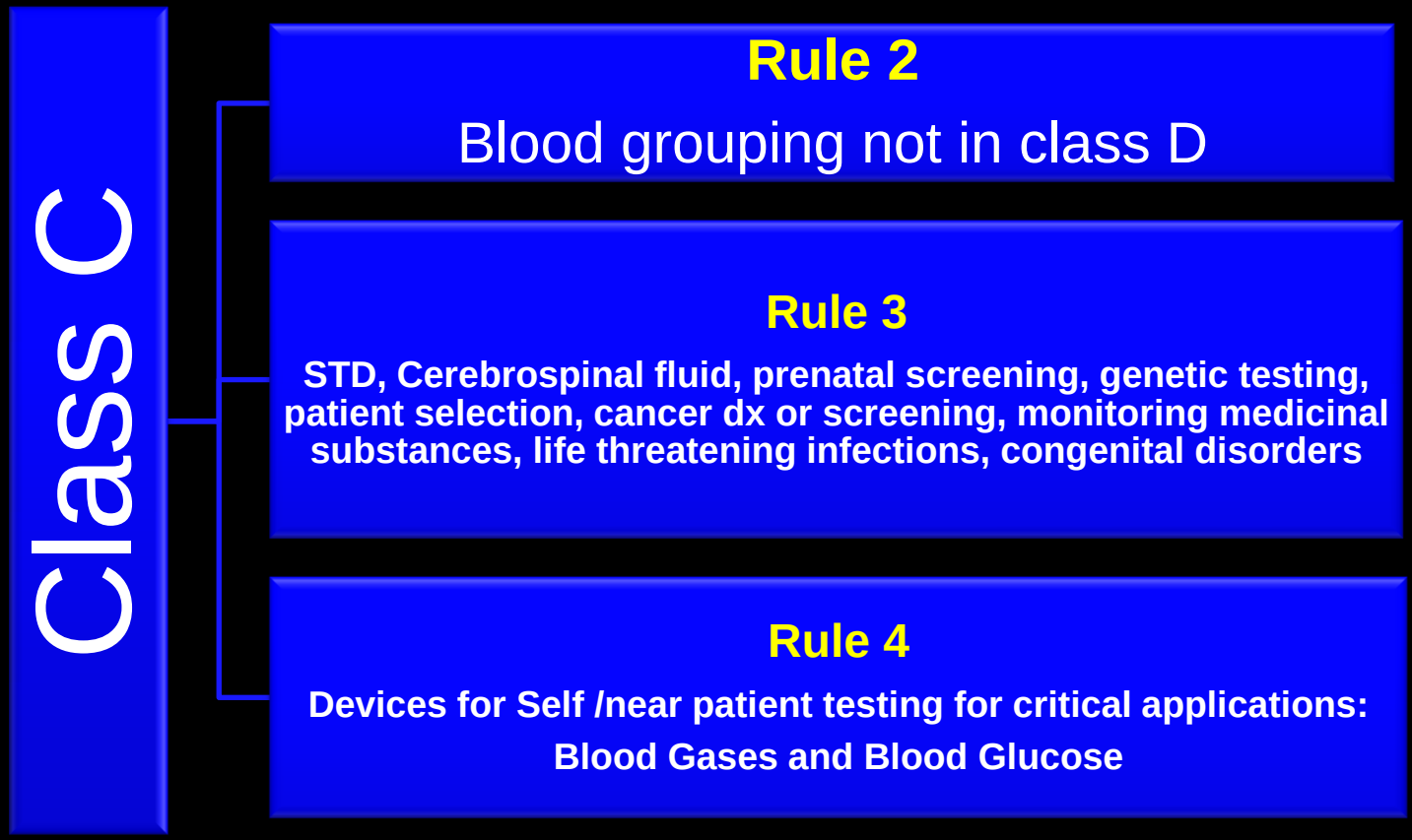
Rules-based classification

List expansion!!

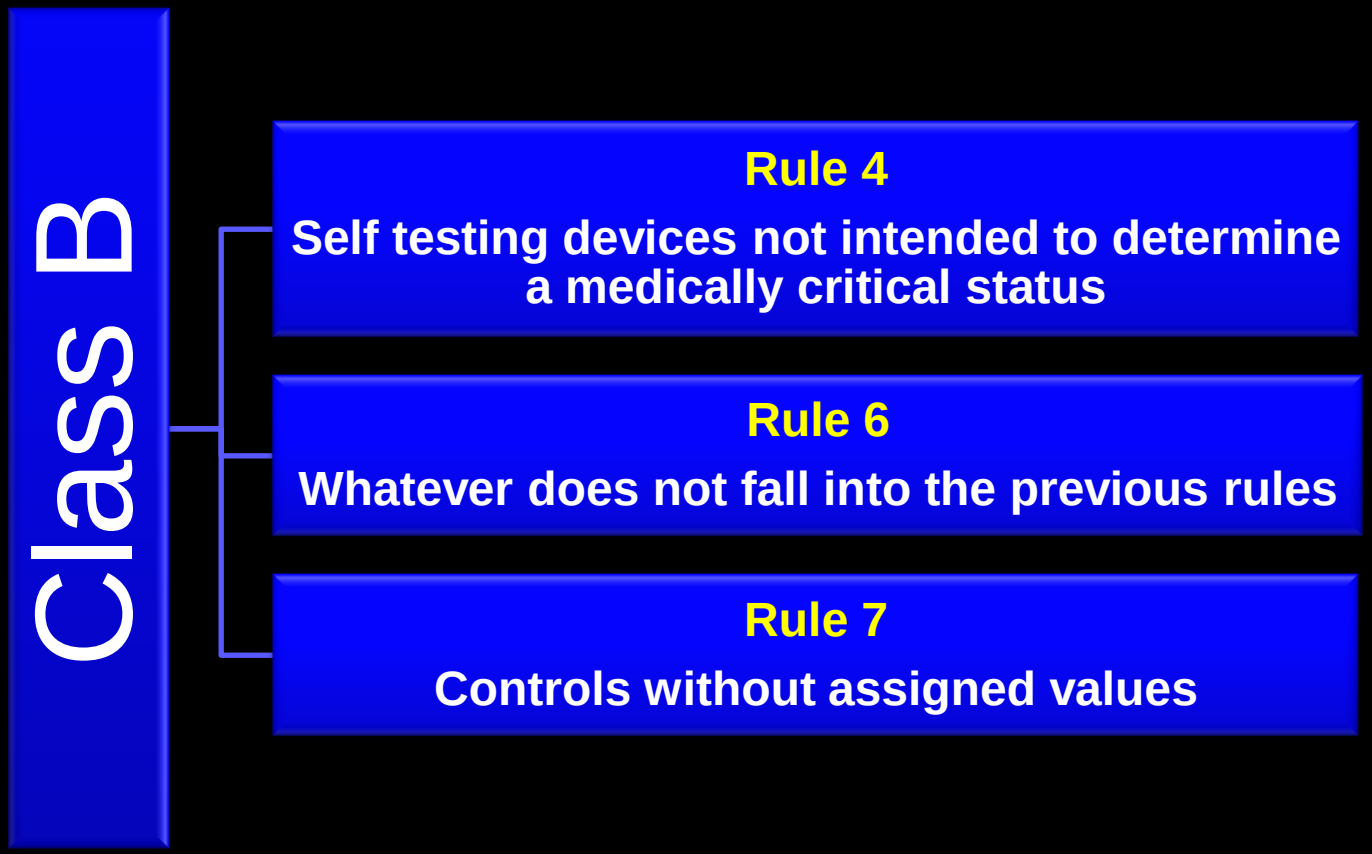
Class D


Class D
Rule 1
Transmissible agents in blood
Detection of life threatening diseases with a high risk of propagation
Rule 2
Blood grouping markers – ABO, Rhesus, Kell, Kidd, Duffy systems

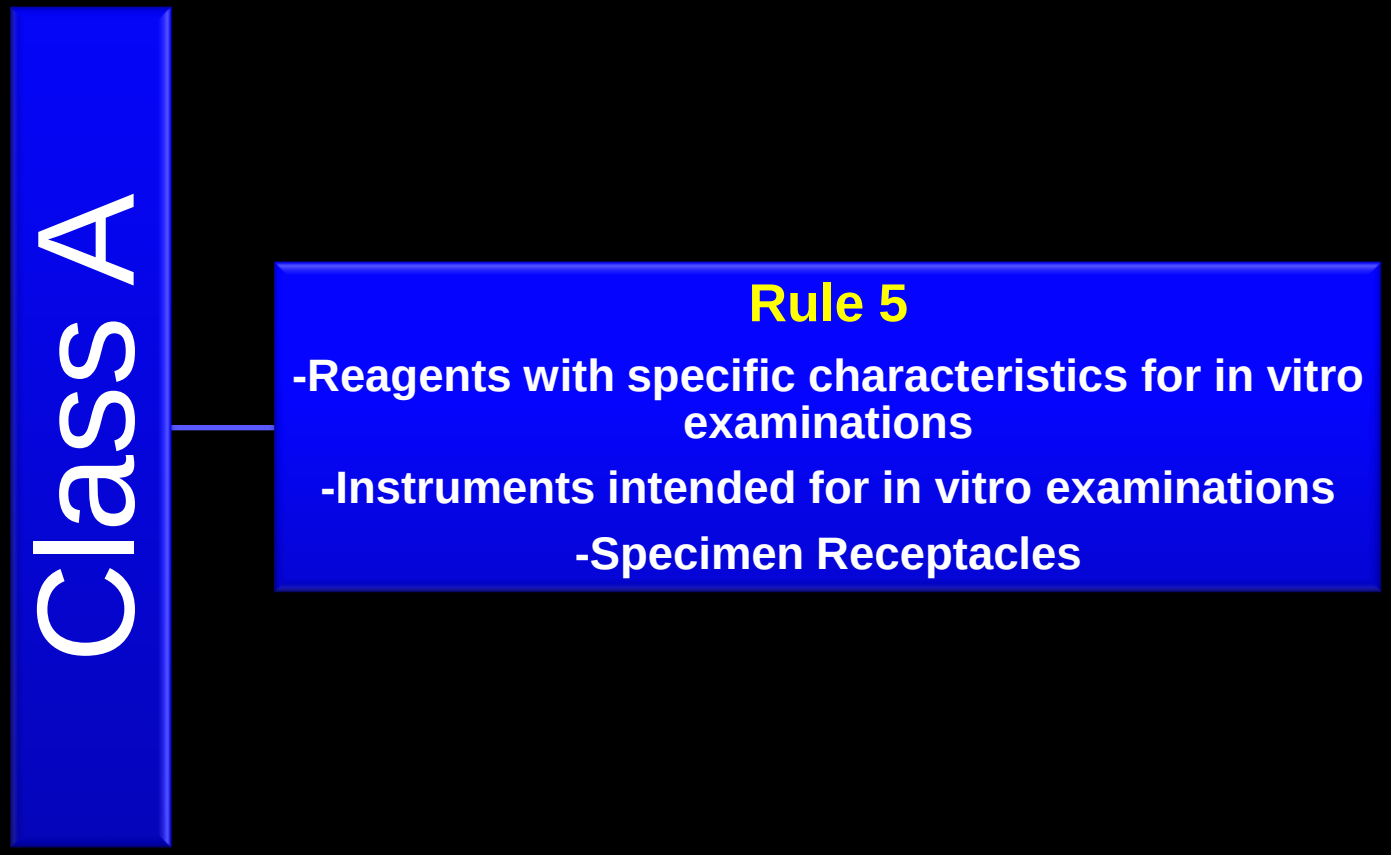
Class C


Class C
Rule 2
Blood grouping not in class D
Rule 3
STD, Cerebrospinal fluid, prenatal screening, genetic testing, patient selection, cancer dx or screening, monitoring medicinal substances, life threatening infections, congenital disorders
Rule 4
Devices for Self /near patient testing for critical applications:
Blood Gases and Blood Glucose

Class B


Class B
Rule 4
Self testing devices not intended to determine a medically critical status
Rule 6
Whatever does not fall into the previous rules
Rule 7
Controls without assigned values

Class A


Class A
Rule 5
-Reagents with specific characteristics for in vitro examinations
-Instruments intended for in vitro examinations
-Specimen Receptacles

Increased demands for IVD reagents Class B

CLASS "B" DEVICE		
Conformity Assessment Element	**Manufacturer Responsibility**	**RA / CAB Responsibility**
Quality Management System (QMS)	Establish and maintain a full QMS or a QMS without design and development controls.	Be satisfied that a current and appropriate QMS is in place or otherwise conduct a QMS audit prior to marketing authorization.
Post Market Surveillance	Establish and maintain an adverse event reporting procedure according to GHTF SG2 guidance.	Be satisfied that a current and appropriate adverse event reporting procedure is in place as part of the QMS.
Technical Documentation	Upon request prepare STED.	Premarket submission normally not required but if requested, receive and conduct a review of the STED to determine conformity to Essential Principles.
Declaration of Conformity	Prepare, sign and submit.	Review and verify compliance with requirements.
Registration of manufacturers and their devices	Perform according to regulatory requirements.	Maintain and verify as appropriate.

STED (Summary Technical Documentation)

Increased demands for IVD reagents Class C

CLASS "C" DEVICE

Conformity Assessment Element	Manufacturer Responsibility	RA / CAB Responsibility
Quality Management System (QMS)	Establish and maintain a full QMS.	Be satisfied that a current and appropriate QMS is in place or otherwise conduct a QMS audit prior to marketing authorization.
Post Market Surveillance	Establish and maintain an adverse event reporting procedure according to GHTF SG2 guidance.	Be satisfied that a current and appropriate adverse event reporting procedure is in place as part of the QMS.
Technical Documentation	Prepare and submit STED for review.	Receive and conduct a premarket review of the STED to determine conformity to Essential Principles.
Declaration of Conformity	Prepare, sign and submit.	Review and verify compliance with requirements.
Registration of manufacturers and their devices	Perform according to regulatory requirements.	Maintain and verify as appropriate.

STED (Summary Technical Documentation)

Public consultation for:

-Special Genetic testing (e.g. predictive etc)
-In-house tests
-Accreditation
-Clinical Validity/utility
-Direct-to-consumer labs
-POCT
-Notifying bodies
-Conditional “CE marking”

European Commission:

HEALTH AND CONSUMERS DIRECTORATE-GENERAL (SANCO)

Consumer Affairs

Cosmetics and Medical devices (B2)

http://ec.europa.eu/health/medical-devices/

Public consultation: 29 June 2010

EFCC-IVD WG: #54 response (161 total responses)

Summary report: 23 February 2011

Medical Devices Expert Group (MDEG)-WG directive draft: 13/2/12

New EFCC response: 16/3/12

New revision proposal: 26/09/12

2 years till acceptance from Commission and Europarliament

5 year transitional period

Controls Mechanisms of the new proposed Regulation

- Common specifications (CS) – Assessment by Reference Labs (Class D)
- Possible additional assessment by SNB or case-by-case assessment by the MDCG (if there is no CS for class D)
- Registration with authorities (all classes)

- Vigilance process (all classes)
- Post-market follow up (all classes)
- Unique Device Identification (UDI) allows for Traceability
- Control of the supply chain added to all devices

Latest developments

New rapporteur for Medical Devices regulation: Glenis Willmott (UK MEP), a former Clinical Chemist!

Same rapporteur for IVDs: Peter Liese (DE MEP), MD in Paediatrics & PhD in Human Genetics

From Sept. 10, 2014 the handling of the two regulations passes to DG Internal Market, Industry, Entrepreneurship & SMEs (from DG SANCO)

The Council presidency passed from Greece to Italy with the hope of the dossier closure before the next presidency (Latvia)

Interesting EuroParliament 1st reading amendments to Commission proposal (24 Oct 2013) were discussed among WG members.

A consensus was reached in most items and in the few challenging ones, we have the following developments from the Greek presidency:

Definitions: Article 1

2. This Regulation shall not apply to:

(a) products for general laboratory use, unless such products, in view of their characteristics, are specifically intended by their manufacturer to be used for *in vitro* diagnostic examination;

(b) invasive sampling devices or those which are directly applied to the human body for the purpose of obtaining a specimen;

(c) ~~higher metrological order~~ ***internationally certified*** reference materials.

(d) materials used for external quality assessment schemes

(e) research-use only products

FDA Guidance for mislabeling as RUO products that are used as IVD:
Products with unproven characteristics and inadequate GMP

Definitions: Article 1 (#2)

This Regulation shall not affect national laws which require that ***inter alia*** certain devices may only be supplied on a medical prescription.

Removal of class D, genetic testing and companion diagnostics specific demand for medical prescription

(6) 'companion diagnostic' means a device specifically intended to select patients with a previously diagnosed condition or predisposition as eligible for a targeted therapy;

(21) 'health institution' means an organisation whose primary purpose is the care or treatment of patients or the promotion of public health;

No exclusion of commercial labs

Definitions: Article 1 (#3)

'*in vitro* diagnostic medical device' means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, software 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 ***process or*** state;
- concerning a congenital abnormality;
- concerning the predisposition to a medical condition or a disease;
- to determine the safety and compatibility with potential recipients;
- to predict treatment response or reactions;
- to define or monitor therapeutic measures.

Specimen receptacles are considered to be *in vitro* diagnostic medical devices. For the purposes of this Regulation, 'specimen receptacle' means 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.

In-house testing

With the exception of Article 59(4) **and the relevant general safety and performance requirements set out in Annex I,** the requirements of this Regulation shall not apply to devices ~~classified as class A, B and C, in accordance with the rules set out in Annex VII, and~~ manufactured and used only within a single health institution, provided **the following conditions are met:**

(a) manufacture and use **of the device** occur solely under ~~the health institution's~~ ***a*** single quality management system, ~~and~~

(b) the health institution is ~~compliant with~~ **accredited to** standard EN ISO 15189 or any other equivalent recognised standard. ~~Member States may require that the health institutions submit to~~

(c) the **recipient patient or patient group's specific needs cannot be met by a device available on the market,**

(d) **the health institution provides information on the use of such devices to their** competent authority**, which shall include a justification of their manufacturing, modification or use.**

+ISO 22870 for POCT

In-house testing (#2)

Member States shall make publically available a list of ***all*** such devices which have been manufactured and used on their territory. **Member States shall retain the right to restrict the manufacture and use of any specific type of such devices in relation to aspects that are not covered by this Regulation** and may make the manufacture and use of the devices concerned subject to further safety requirements.

~~Devices classified as class D in accordance with the rules set out in Annex VII, even if manufactured and used within a single health institution, shall comply with the requirements of this Regulation. However, the provisions regarding CE marking set out in Article 16 and the obligations referred to in Articles 21 to 25 shall not apply to those devices.~~

~~The Commission shall be empowered to adopt delegated acts in accordance with Article 85, amending or supplementing, in the light of technical progress and considering the intended users or patients, the general safety and performance requirements set out in Annex I, including the information supplied by the manufacturer.~~

These provisions do not apply to devices which are manufactured on an industrial scale and which are used within the framework of a commercial diagnostic service.

Article 4 Genetic testing

Liese's amendment backed by U. of Passau Opinion/OECD but was not endorsed by ESHG/Alliance

"It tries to regulate medical practice via device regulation. Before a genetic test is even ordered! Unworkable: regulatory bodies will have to visit genetics clinics! It will be appealed in the EU Court of Justice"

1. A device may only be used for the purpose of a genetic test in the premises of an accredited according to ISO 15189 and 17025 or equivalent standard(s) labouratory if the referral is granted by persons admitted to the medical profession under the applicable national legislation after a personal consultation.

2. A device may be used for purposes of a genetic test only in a way that the rights, safety and well-being of the subjects are protected and that the clinical data generated in the course of the genetic testing are going to be reliable and robust.

3. Information: Before using a device for the purpose of a genetic test the person mentioned in paragraph 1 shall provide the person concerned with appropriate information on the nature, the significance and the implications of the genetic test.

Article 4 Genetic testing (#2)

4. Genetic counselling: Appropriate genetic counselling is mandatory before using a device for the purpose of predictive and prenatal testing and after a genetic condition has been diagnosed. It shall include medical, ethical, social, psychological and legal aspects and has to be addressed by physicians, geneticists and bio-scientists qualified in genetic counselling.

   The form and extent of this genetic counselling shall be defined according to the implications of the results of the test and their significance for the person or the members of his or her family, including possible implications concerning procreation choices.

5. Consent: A device may only be used for the purpose of a genetic test after the person concerned has given free and informed consent to it. The consent has to be given explicitly and in writing. It can be revoked at any time in writing or orally.

Article 4 Genetic testing (#3)

6. Testing of minors: In case of minors the informed consent of the parents or legal representative shall be obtained; consent must represent the minor's presumed will and may be revoked at any time, without detriment to the minor. In case of incapacitated adults not able to give informed legal consent, the informed consent of the legal representative shall be obtained; consent must represent the presumed will and may be revoked at any time, without detriment to the person.

7. A device may only be used for the determination of sex in connection with prenatal diagnosis, if the determination fulfils a medical purpose and if there is a risk of serious gender specific hereditary diseases. By way of derogation from Article 2(1) and (2) this also applies to products which are not intended to fulfil a specific medical purpose.

8. The direct-to-patient making available on the market of genetic self-test devices is prohibited.

9. The above provisions on the use of devices for the purpose of genetic tests do not prevent the Member States from maintaining or introducing for reasons of health protection or reasons of public health and order more stringent national legislation in this field

New article for promotion

Article 20a

Promotion

1. Where medical devices are being promoted, no gifts, pecuniary advantages or benefits in kind may be supplied, offered, promised or accepted, unless they are inexpensive and relevant to the practice of medicine.
2. Hospitality at events for purely professional and scientific purposes or at sales promotion events shall always be strictly limited to the main objective of the event and to what is strictly necessary to attend said event.
3. Services rendered by healthcare professionals as part of the marketing or promotion of medical devices, shall be based on a written agreement detailing at least the exact nature of the services and remuneration. Remuneration shall be proportionate to the services rendered.
4. Existing measures and trade practices in Member States relating to prices, margins and discounts shall not be affected by paragraphs 1, 2 and 3. Importers shall ensure that, while a device is under their responsibility, storage or transport conditions do not jeopardise its compliance with the general safety and performance requirements set out in Annex I.