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Comments from the Danish Medical Society in collaboration with the Danish Society for Clinical Biochemistry and the Danish Society for Clinical Immunology.

QUESTIONNAIRE

1. Classification

Question 1:

- Would you consider the adoption of a **risk-based classification** for *in vitro* diagnostic medical devices as an improvement of the current European regulatory framework?
- Are you aware of any **consequences** for the protection of **public health**?
- Can you provide **economic data** linked to a change-over to this GHTF classification system?

A risk-based classification of IVD-equipment is an improvement if the requirements are made in relation to implementation and use of the equipment is graded accordingly.

2. Conformity assessment procedure

Question 2:

In the context of a possible adoption of a **risk-based classification** according to the **GHTF model** (see above 1.) do you see a need for amending the current conformity assessment procedures for *in vitro* diagnostic medical devices?

Question 3:

If yes, in your view which are the **conformity assessment procedures** that should be **deleted or amended** and **why**?

Question 4:

Would you consider appropriate to **require for all IVDs**, except for those in class A of the GHTF classification, at least the **pre-market control** of the manufacturer's **quality management system** by a third party as laid down in GHTF/SG1/N046:2008?

Question 5:

In the context of the "**batch release verification**", do you consider that a **control of each batch** of manufactured **high-risk IVDs** should be required prior to their placing on the market?

If yes, what would be the **purpose of batch release verification** and **which IVDs** should be subject to such a control?

If yes, **how** (testing, verification of the results of the tests) and **by whom** (manufacturer under the control of notified bodies, notified bodies, independent laboratories) these controls should be performed?

High risk IVDs should be subject to control by the manufacturer before release, but this will not exempt the recipient in terms of receiver control of critical equipment.

Question 6:

Should the use of **Common Technical Specifications** (CTS) be maintained for **high-risk IVDs**? Should CTS also be adopted for other IVDs?

"Common Technical Specifications" only have limited value in relation to clinical immunological procedures.

3. Scope

3.1 Specific exemption for "in-house tests"

Question 7:

Would it be necessary **to maintain** the exemption provided for by article 1(5) of Directive 98/79/EC and why?

Yes, it is necessary to maintain the exemption for in-house tests.

Current practices with regards to in-house tests and research use only tests: In-house tests are widely used for diagnosis and control of orphan diseases (e.g. haemophilia, porphyrias, rare endocrine syndromes, spherocytosis, specific dyslipidemic syndromes), molecular diagnosis of genetic diseases, drug analyses, screening for hemoglobinopathies, renal stone analysis and diagnosis of B12 deficiency (Methylmalonic acid). Generally, CE-marked tests are used if they are available. The request for CE-marking of in-house tests may seriously hinder the necessary development of new tests for orphan diseases, molecular diagnosis of genetic diseases and drug analyses.

The volume of tests affected by the exemption: Up to 5 % of the tests offered by clinical biochemistry laboratories at University Hospitals may consist of in-house tests. However, expenditure, workload, and medical impact are much higher.

The types of tests which may be affected grouped according to disease/condition: Orphan diseases/genetic diseases, drug monitoring, and others.

Implications for patient outcomes: Laboratory costs will escalate and many of the genetic tests will cease to be available in Denmark/Europe. Patients must wait longer time for diagnoses.

Quality implications: increased expenditure of tests due to CE-marking is not necessarily equal to better quality of tests. E.g. genetic tests may as a consequence of increased cost be performed in laboratories outside Denmark/EU where regulations are less stringent and quality is difficult to monitor.

Implications and availability of commercial alternatives: For the majority of in-house tests used there are presently no commercial alternatives.

Any difficulties associated with a requirement to CE-mark all tests: Discrimination against people with orphan diseases

It is absolutely necessary to maintain the exemption for utensils used locally in certain areas in clinical immunology, including:

1. Serological test of tissue, thrombocytes and blood.
2. Cellular reagents with reverse typing.
3. Internal serological and cellular controls.
4. Cellular panels for specification of antibody-reactivity
5. Reagents for genetic tests developed locally.

In these instances one depends completely on locally manufactured reagents and cellular material.

In certain areas it is necessary to disregard the current regulative since circulation of cells with rare phenotypical characteristics between laboratories in the so-called SCARF-collaboration cannot take place within the activities permitted by the regulative.

Question 8:

If the exemption provided for by article 1(5) of Directive 98/79/EC **should be clarified or limited**, which of the following items you would consider as appropriate in order to clarify the scope of this exemption and ensure a high level of safety:

None of these items are appropriate. In general, in-house methods are thoroughly validated before use in Danish laboratories.

There is no need for a limitation of article 1(5). On the contrary, the restrictions should be alleviated where needed – e.g. in relation to SCARF and for external proficiency testing where circulation is an implicit part of the analysis design and control. Item 1 is therefore the one that matches best the needs of the clinical immunological departments.

Item 1:

Better **define the concepts** of "in-house test", "health institution", "premises of a manufacture or premises in the immediate vicinity". Could you suggest an appropriate definition for these terms?

Item 2:

Require that all "in-house tests" fulfil the **essential requirements** of the Directive 98/79/EC, **without being subject to a CE marking**?

Item 3:

Require that all **high risk** "in-house tests" are **excluded from the exemption** provided for by article 1(5) of Directive 98/79/EC and then have to fulfil the essential requirements of the Directive 98/79/EC including the involvement of a notified body?

Item 4:

Submit the health institutions and premises referred to in Article 1(5) of Directive 98/79/EC that manufacture "in house tests" to **accreditation**, based on ISO 15189, or **equivalent regulation** at national level?

Please indicate one or more items that you would consider **as appropriate** while explaining **why** you consider these items as appropriate and providing **data** where possible.

In case you consider none of these items as appropriate or if there are, in your opinion, **other options** that are appropriate please indicate them.

Question 9:

If the exemption provided for by article 1(5) of Directive 98/79/EC **should not be maintained**, would you consider it necessary to **exempt *in vitro* diagnostic medical devices** intended for **diagnosis and monitoring of diseases or conditions affecting not more than 5 in 10,000 persons in the European Union** from the scope of the IVD Directive and, if yes, why?

Exemption based on disease frequency is not appropriate, as diseases may be rare in one region while frequent in another region (e.g. thalassemia).

3.2 Genetic tests

The interpretation of the scope of Directive 98/79/EC is that **only genetic tests that have a medical purpose are covered by this Directive**, e.g. prenatal diagnostic tests, diagnostic tests of diseases, tests intended to assess the answer to a medical treatment, tests used in conjunction with the use of a specific medicinal product, pharmacogenomic tests etc.

However beside these tests for which a direct medical purpose can be established, the medical purpose might be not so clear for some predictive tests, lifestyle tests, nutrigenetic tests, etc. This might lead to different interpretation on the qualification of these products within the European Union.

In addition to the above there are **increasing concerns** regarding genetic tests (*e.g.* direct to consumer genetic tests, predictive tests), including genetic tests without a clear medical purpose. These concerns are related among others to the lack of quality, lack of scientific evidence and lack of clinical validity or clinical utility of these tests.

Question 10:

Do you see a need for a **clarification of the scope of Directive 98/79/EC** to make clear that it covers **all genetic tests** that have a **direct or indirect** medical purpose while clarifying that tests without any direct or indirect medical purpose remain outside the scope of the Directive 98/79/EC.

If you consider that there is a need to clarify the scope of Directive 98/79/EC as regards genetic tests, which of the following items would you consider as appropriate:

Item 1:

Extend the scope to **all genetic tests** by adding a specific indent in the definition of *in vitro* diagnostic medical devices regarding devices which pursue the purpose of providing information concerning “**results obtained by analysis of the genome**”. Should, in this case, an **exclusion** be introduced in the Directive 98/79/EC **as regards some categories** of tests (negative list) *e.g.* paternity, DNA comparison?

Item 2:

Clarify that tests, including genetic tests, with a **direct or indirect medical purpose** are included within the scope of Directive 98/79/EC.

Question 11:

Do you see a need to create **additional requirements or restrictions for direct-to-consumer genetic tests** in order to ensure a better level of health protection? If yes, on which aspects?

Genetic procedures in clinical immunology are extremely complex and should be accompanied by explanations and guidance offered by trained, professional staff. Therefore, direct-to-consumer genetic tests should not be accepted.

3.3 Diagnostic services

There are an increasing number of tests which are performed within an economic operator's facility (within the EU or outside) **without placing the *in vitro* diagnostic medical devices on the market**. The economic operator receives the body specimen and provides the result either directly to the patient or to a physician. Sometimes, different operators act at different steps in order to obtain the results of the test: specimen reception, specimen tests, statistical analysis, results. Despite Recital 11 and Article 9(13) of Directive 98/79/EC¹ it may not always be clear that IVDs used in such a situation are subject to Directive 98/79/EC. There are **increasing concerns** regarding the validity and the reliability of the results of such tests and the understanding of the result by lay users. In principle, these tests performed by the manufacturer should be subject to the **same requirements** than *in vitro* diagnostic medical devices that are placed on the market.

Question 12:

Do you see a need to **amend the definition of "putting into service"** to make it clear that it covers also the *in vitro* diagnostic medical devices that are not placed on the market but used for the delivery of results within the Community?

It is likely that an expansion of the requirements in relation to "unauthorized" sellers of diagnostic procedures will improve safety and quality in several areas.

Question 13:

Do you see a need to **introduce other specific requirements** for tests used for diagnostic services, especially when the results of the tests are provided directly to consumers, such as minimum requirements for advertising?

The requirements in relation to advertising should be just as strict as those regarding 'direct to consumers' diagnostic tests with regards to professional interpretation and guidance.

3.4 Point-of-care / near-patient *in vitro* diagnostic medical devices

There is a growing number of tests which are **performed outside a laboratory environment** but **near to a patient** by a **healthcare professional**, who is not necessarily a laboratory professional, in order to make a diagnosis and to determine the appropriate treatment. These tests are often referred to as "point-of-care" or "near-patient" tests².

¹ Article 9(13) Directive 98/79/EC states: "The provisions of this Article shall apply accordingly to any natural or legal person who manufacturers devices covered by this Directive and, without placing them on the market, puts them into service and uses them in the context of his professional activity."

² GHTF/SG1/N045:2008 regarding Principles of In Vitro Diagnostic (IVD) Medical Devices Classification (see above footnote 6) defines "near-patient testing" as "testing performed outside a laboratory environment by a healthcare professional not necessarily a laboratory professional, generally near to, or at the side of, the patient".

Question 14:

Do you see a need to **add specific requirements** for "**point of care**" or "**near-patient**" *in vitro* diagnostic medical devices? If yes, regarding which **aspects** (*e.g.* information supplied by the manufacturer)?

It appears that there are no specific problems related to the PoC-tests provided that quality control and calibration are performed in the same way as other types of analyzes.

4. Clinical evidence

The essential requirements of Directive 98/79/EC foresee requirements regarding the performances of *in vitro* diagnostic medical devices. In particular, the **demonstration of performance** should include, where appropriate analytical sensitivity, diagnostic sensitivity, analytical specificity, diagnostic specificity, accuracy, repeatability, reproducibility, including control of known relevant interference, and limits of detection, stated by the manufacturer. These requirements are a mix of analytical and clinical requirements.

Question 15:

Do you see a need to **further clarify the requirements regarding clinical evidence** for *in vitro* diagnostic medical devices?³

No.

4.1 Clinical validity

The **clinical validity**⁴ is the demonstration of the performance characteristics supporting the **intended use** of the *in vitro* diagnostic medical devices and includes diagnostic sensitivity, diagnostic specificity based on the true disease status of the patient and negative and positive predictive values based on the prevalence of the disease. These two last elements (negative and positive predictive values based on the prevalence of the disease) are currently not clearly mentioned in the Directive 98/79/EC.

Question 16:

On the basis of the above, do you see a need to **extend the requirements** regarding the demonstration of **the clinical validity** in Directive 98/79/EC?

No.

4.2 Clinical utility

Beside the notion of clinical validity, the notion of **clinical utility**⁵ is the demonstration of the potential usefulness and added value to patient management decision-making. The notion of clinical utility for the purpose of this document **does not include cost/benefit assessment, reimbursement issues and/or health economics issues**. If a test has a

³ The GHTF is currently working on a guidance document on clinical evidence for IVDs.

⁴ The Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes of 27 November 2008 distinguishes between scientific validity and clinical validity. See <http://conventions.coe.int/Treaty/EN/Treaties/Html/203.htm>

⁵ The Additional Protocol mentioned in the previous footnote also introduces the notion of clinical utility.

utility, it means that the results provide valuable information for the purpose of making decisions about effective treatment or preventive strategies.

Question 17:

In the context of the above, do you see a need to **require the demonstration of the clinical utility** of the parameter in Directive 98/79/EC? If yes, how should the clinical utility be demonstrated?

No.

5. Others

5.1 “Conditional CE marking”

For unmet medical needs of patients, for example in the case of rare diseases or in emergency situations such as a pandemic, it might be useful to introduce a mechanism which can allow a rapid market access of certain IVDs subject to certain conditions. Currently, Article 9(12) of Directive 98/79/EC makes provision that Member States can accept IVDs in their respective territories without proper conformity assessment procedure if this is justified in the interest of public health protection. Instead of such national solutions, a “**conditional CE marking**” might be allowed for a limited period of time (*e.g.* one year renewable) and subject to specific obligations imposed on the manufacturer with a view to confirm the safety and performances of the tests.

Question 18

Would you consider the possibility of a **conditional CE marking** in certain situations useful? Which situations would you think of and which conditions, including procedural requirements, would you consider necessary?

Yes, for instance in situations with urgent requirement of diagnostic tests. Here a “conditioned CE-certification” may be of value.

5.2. Companion in vitro diagnostic medical devices (*e.g. pharmacogenomic assays, biomarker assays*)

There are a growing number of tests which are **developed** and/or **used** in **direct combination with specific medicinal products** or which are **co-developed** with new medicinal products. These tests may be used for the selection of patients suitable for the respective medication, for optimal and individualized dosing of medicinal products, for the exclusion of populations expected to suffer from severe adverse side effects and / or other medicinal products-related indications. Currently, most companion diagnostics are self-certified by the IVD manufacturer.

Question 19:

Which options do you see to guarantee a high quality of IVD medical devices used as **companion diagnostics**?

The requirements made on companion diagnostics should be equal to those made on all other diagnostic tests.

