EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Consumer Affairs
Cosmetics and Medical devices

Brussels, 29 June 2010

REVISION OF DIRECTIVE 98/79/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL OF 27 OCTOBER 1998 ON *IN VITRO* DIAGNOSTIC MEDICAL DEVICES

PUBLIC CONSULTATION

Rules relating to the safety and performance of medical devices were harmonised in the EU with Council Directive 90/385/EEC relating to **active implantable medical devices,** Directive 93/42/EEC concerning **medical devices** and Directive 98/79/EC on ***in vitro* diagnostic medical devices**.

In the context of the simplification of the regulatory environment, and in the light of the technological progress and of emerging weaknesses identified regarding key elements of the regulatory framework, a public consultation was launched in 2008 on the **Recast of the Medical Devices Directives**[1].

Many responses received to the public consultation underlined **the need to revise Directive 98/79/EC**. In fact, Directive 98/79/EC has not been substantially amended since its adoption in 1998[2]. Since then the sector has significantly evolved technologically. In addition, the two other medical devices Directives were revised by Directive 2007/47/EC[3], the New Legislative Framework for the Marketing of Products[4] was adopted in 2008 and the Global Harmonization Task Force for medical devices (GHTF) elaborated new guidelines in the field of IVD medical devices[5].

Taking into account the specificities of *in vitro* diagnostic medical devices, it appears appropriate to launch this **public consultation** targeted on **specific issues** related to *in vitro* diagnostic

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1 http://ec.europa.eu/enterprise/sectors/medical-devices/documents/revision/index_en.htm

2 Only Articles 6 and 7 of Directive 98/79/EC were amended by Regulation (EC) No 1882/2003.

3 http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:247:0021:0055:en:PDF

4 http://ec.europa.eu/enterprise/policies/single-market-goods/regulatory-policies-common-rules-for-products/new-legislative-framework/index_en.htm

5 http://www.ghtf.org/

Commission européenne/Europese Commissie, 1049 Bruxelles/Brussel, BELGIQUE/BELGIË - Tel. +32 22991111
Office: BREY 10/180 - Tel. direct line +32 229-55738 - Fax +32 229-66467
Sanco-cosmetics-and-medical-devices@ec.europa.eu

medical devices in order to complement the above mentioned public consultation. Please note that possible amendments of general aspects such as designation and monitoring of Notified Bodies, vigilance, market surveillance, need for further centralisation etc. which are currently under discussion in the framework of the recast of Directives 90/385/EEC and 93/42/EEC will apply, *mutatis mutandis*, also to the revision of the IVD Directive.

Answers are expected as regards the possible improvement which the possible options may bring about. The Commission also seeks to obtain data concerning the likely socio-economic impact of the possible changes and in particular the impact on the **protection of health and safety** of patients, healthcare professionals or, where applicable, other users, on **the functioning of the internal market** and on the **competitiveness and innovativeness** of the industry, in particular small and medium-sized enterprises.

Therefore, to the greatest extent possible, respondents should include in their answers data corresponding to these different aspects (social and economic data) supported, where possible, by an evaluation of actual or estimated costs (expressed in figures such as cost per device, cost per manufacturer, cost per national authority, cost per hour, cost per man-day etc.), and by other relevant quantitative figures.

Any comments and information on this public consultation should be submitted by mail, fax or e-mail by 15 September 2010 at the latest to:

European Commission
Health and Consumers Directorate-General (DG SANCO)
Unit SANCO B2, Cosmetics and Medical Devices
B-1049 Brussels, Belgium
Fax: 00 32 (0) 2 296 64 67
e-mail: SANCO-IVD-REVISION@ec.europa.eu

Respondents should indicate **the interests that they represent** (i.e. whether they are a national authority, patient, health professional, consumer, notified body, industry, trade association, academia, etc.).

If they are a company, **the approximate size** (turnover, employees) and the main market (product market and geographical market) should be indicated.

Submissions will be published on the "medical devices" website of the European Commission.

Respondents should indicate whether they wish the Commission to treat their submission as **confidential** by clearly indicating the word "confidential" on the first page of the contribution. Please note that a standard confidentiality disclaimer in the e-mail transmission will not be considered as a request to treat the submission as confidential

QUESTIONNAIRE

1. Classification

A specific question raised in the public consultation launched in 2008 was the **implementation of a risk-based classification**, following the model of the Global Harmonization Task Force for medical devices (GHTF) for *in vitro* diagnostic medical devices. The GHTF classification rules for IVDs are laid down in the guidance document GHTF/SG1/N045:2008 entitled "Principles of In Vitro Diagnostic (IVD) Medical Devices Classification" adopted on 19th February 2008[6]. A majority of stakeholders were in favour of such a risk-based classification in order to improve the robustness to technological change. Such classification rules would replace the current listing of high-risk IVDs in Annex II of Directive 98/79/EC.

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?

2. Conformity assessment procedure

The GHTF guidance document GHTF/SG1/N046:2008 entitled "Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices", adopted on 31 July 2008[7], sets out the elements of **conformity assessment** applicable to the different classes of IVDs. In addition, the current IVD Directive requires the verification of manufactured devices covered by Annex II, List A ("batch release verification"). However the implementation of this verification does not seem to be uniform. For IVDs listed in Annex II, the IVD Directive also makes provision for the adoption of Common Technical Specification (CTS) which shall establish appropriate performance evaluation and re-evaluation criteria, batch release criteria, reference methods and reference materials.

[6] http://www.ghtf.org/documents/sg1/sg1final_n045.pdf

[7] http://www.ghtf.org/documents/sg1/sg1final_n046.pdf

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?

Question 6:

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

3. Scope

3.1 Specific exemption for "in-house tests"

Article 1(5) of Directive 98/79/EC makes provision for an exemption for devices manufactured and used only within the same health institution and on the premises of their manufacture or used on premises in the immediate vicinity without having been transferred to another legal entity. These tests are referred below as "in-house tests".

It appears that **this exemption could be reviewed** in particular to ensure a high safety standard also for "in-house tests" and to prevent unfair competition between CE marked *in vitro* diagnostic medical devices and "in-house tests". On the other hand, for certain diseases, only "in-house tests" may be available for diagnosis. It is therefore necessary to determine if there is a need to clarify or limit the scope of this exemption and/or to submit some "in-house tests" to certain requirements of Directive 98/79/EC.

Question 7:

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

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:

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?

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?

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/EC[8] it may not always be clear that IVD's 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?

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?

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" tests[9].

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)?

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[8] 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."

[9] 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".

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?[10]

4.1 Clinical validity

The **clinical validity**[11] 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?

4.2 Clinical utility

Beside the notion of clinical validity, the notion of **clinical utility**[12] 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 utility, it means that the results provide valuable information for the purpose of making decisions about effective treatment or preventive strategies.

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[10] The GHTF is currently working on a guidance document on clinical evidence for IVDs.

[11] 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

[12] The Additional Protocol mentioned in the previous footnote also introduces the notion of clinical utility.

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?

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?

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**?