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. 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?
Yes.

– Are you aware of any consequences for the protection of public health?
This would enable a dynamic response to new diagnostic challenges for 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, 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.

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?

Yes, there is a gap of adequate assessment procedures between devices for self testing (e.g. III.6) and annex II list B (e.g. IV). This gap does not correspond to any risk classification of IVD medical devices.
Question 3:
If yes, in your view which are the conformity assessment procedures that should be deleted or amended and why?

Annex V can be deleted, since there is obviously no need in practice for IVD-products. This applies as long as reagents are involved. As soon as instruments are affected, a need may arise.

An amendment of a procedure would be helpful in the sense of question 2, e.g. the inspection of production / testing of devices at the manufacturer’s site using the respective parts of the quality system.

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?

Yes, this is considered appropriate.

For all IVD medical devices (also for class A) a pre-market conformity assessment must be requested. This assessment must contain the following elements:

- quality system of the manufacturer
- demonstration of calibration hierarchy and metrological traceability
- analytical performance of the system
- intended clinical use of the test

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?

For GHTF class C and D (high individual risk) a batch release verification should be mandatory prior market placing and on a regular basis (once a year) also when already on the market.

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

The purpose of this batch release is to keep the quality of the ivd product constant.

The following only exemplarily shown IVDs should be included in the verification: blood glucose self-testing, blood coagulation self-testing, rubella testing in pregnancy; HLA typing, AB0 blood grouping, Rh testing; HIV, HepB, HepC blood donor screening.

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?

The verification of results and protocols should be done by independent notified bodies.
in collaboration with accredited reference laboratories following the rules released by the JCTLM of the BIPM (http://www.bipm.org/en/committees/jc/jctlm/) or following local rules comparable to the recommended rules.

Question 6:
Should the use of Common Technical Specifications (CTS) be maintained for high risk IVDs? Should CTS also be adopted for other IVDs?

In order to reduce heterogeneity and to guarantee a high level of quality, CTS are useful for high risk IVDs. However, periodic review of CTS is required and appropriate procedures should be defined for this purpose (which experts are involved, opportunities for input by stakeholders, etc.)

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?

The exemption should be maintained, but limited in relation to high risk IVDs.

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?

„In house tests“: validated tests used for clinical diagnostic purposes in a defined health institution (eg university hospital, regional hospital) and developed according to scientific standards by a respective research unit in this hospital, which has demonstrated analytical competence.

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?
Yes, they should fulfill the essential requirements; the high risk one’s should undergo 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?

Yes.

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?

This would be a reasonable approach.

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?

NA, Article 1 (5) to be maintained.

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?

Not yet determined.

**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.

Yes, all tests should be included. Genetic tests (tests using molecular biology technique) provided by laboratory professionals are used for the following medical purpose and should be included in the Directive:

- Prenatal diagnosis
- Risk assessment of diseases
- Monitoring of malignant diseases
- Pharmacogenomomics/Pharmacogenetics
- Detection of viral and bacterial nucleic acids for infectious diseases

**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?

Yes, of course. Genetic tests provided commercially for „life style“ or prediction of a certain condition (e.g. risk of myocardial infarction, etc) should be restricted. Only after a proper scientific and evidence-based investigation (see example above: Question 10, Item 1) these kinds of tests should come to the market after authorisation by a respective body (IVD/CE).

**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/ECs 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
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?

Especially these diagnostic medical devices (tests) used by commercial laboratories used for a kind of patient service, which are not on the diagnostic market, must fulfil the same regulatory requirements like CE-labelled and/or „in house manufactured tests“. Tests applied on patient samples must be under the Directive.

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?

All tests used by diagnostic services must fulfil all the requirements of the Directive (see above)! A direct communication of test results to a patient must be also seen in the shadow of the local "Ärztegesetz". We absolutely not recommend that services provide direct test results to patients. There must always be secured that patients are informed by his medical professional (laboratory medicine, clinical pathologist, medical specialist, practitioner) and not by a "service".

**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.

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)?

Of course we see a heavy need for specific requirements. POCT medical devices are used by medical professionals (no specialists in laboratory medicine/biopathology or laboratory techniques) and by patients. For these devices specific requirements and regulations to be followed and authorized in the pre-market phase are needed. In addition to the handling of these devices for the end-user the analytical specifications (linearity, sensitivity, specificity, interferences, matrix, calibration of the device, demonstration of traceability) must be given. For use of POCT in medical institutions such as intensive care units, special regulatory for quality control, training should be mandatory under the auspices of a medical laboratory of the Institution. POCT should always be referred to standard tests used in the medical laboratory!
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?

For demonstration of performance analytical and clinical information has to be provided by industry to the end-user. This is nowadays not the case!

In addition to the points listed for the analytical performance (analytical sensitivity, diagnostic sensitivity, analytical specificity, diagnostic specificity, accuracy, repeatability, reproducibility, including interference, limits of detection) linearity, matrix to be used, the traceability chain for value assignment are essential for appropriate performance. For the appropriate calibration of routine diagnostic tests the methodological principles of traceability by using high order measurement procedures and certified reference materials as promoted by the BIPM/IFCC/ILAC Joint Committee of Traceability in Laboratory Medicine (JCTLM) must be followed. It is envisaged that in the edition of the Directive this point is more stringent.

http://www.bipm.org/en/committees/jc/jctlm/

The declaration of the proposed clinical use and the clinical performance and clinical utility of an IVD medical device based on scientific publications and evidence have to be inserted in the enclosure of the test.

4.1 Clinical validity
The **clinical validity** 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?

It is agreed that the clinical validity of an IVD medical device should also be covered by the Directive. (see above question 15). But it has to be emphasized that positive and negative predictive value is not useful for classical clinical chemistry determination f.e. creatinin, potassium …
4.2 Clinical utility
Beside the notion of clinical validity, the notion of clinical utility 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.

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?

Yes this has to be demonstrated by the manufacturer and established in a cooperation between manufacturers and the scientific community as far as possible.

For the systematic treatment of clinical evidence in the recast of the IVD-Directive we consider a need for the following 3 elements:

1) The clarification and possibly enrichment of the concepts constituting the “clinical” and analytical essential requirements, including clinical utility and clinical diagnostic performance. The evolving GHTF drafts should be used as a help.
2) A continuous process of (clinical) performance evaluation of IVDs (adapted to the kind of IVDs; with corresponding documentation; to be easily implemented within the QM-systems; the continuous process contributes to solve the problem of the changing "state of the art")
3) A better characterization of performance evaluation studies as an important source of clinical evidence besides literature review and lab/clinical experience (to assure proper ethical, scientific and procedural/administrative conduct of studies; to assure validity of genetic and predictive tests; to better address new interfaces with pharmaceutical sector like biomarkers, responder/susceptibility status for pharmaceuticals, personalized medicine etc). A differentiation should be made there with regard to high/low risk scenarios, as eg foreseen in current GHTF drafts.

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?
"Conditional CE marketing" seems not to be useful. Present national regulations for this purpose seem to be sufficient!

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**?

**Not yet determined.**