EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Consumer Affairs
Cosmetics and Medical devices

Brussels, 23 February 2011

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

SUMMARY OF RESPONSES TO THE PUBLIC CONSULTATION

I. Introduction

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]. This public consultation was mainly focused on horizontal issues regarding the revision of the legal framework for medical devices. Many responses received to the public consultation underlined **the need to revise some specific aspects of Directive 98/79/EC**.

In June 2010, the Commission launched a public consultation targeted on issues related to *in vitro* diagnostic medical devices.

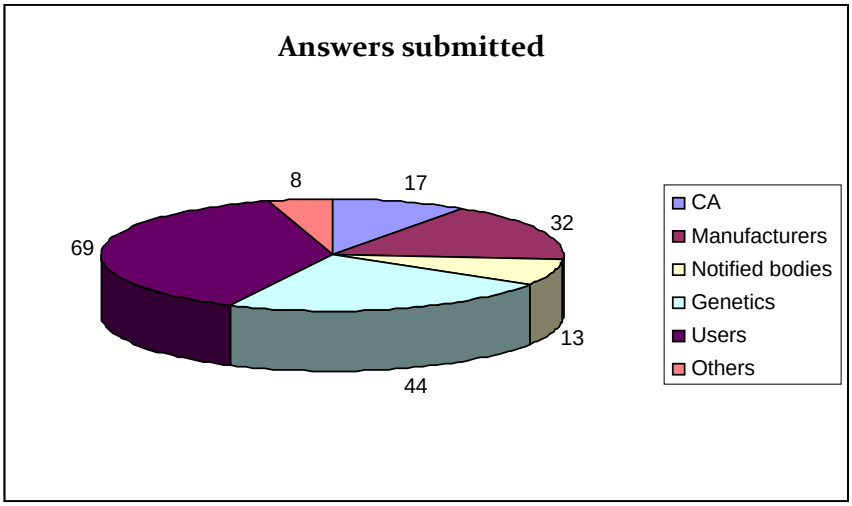
The stakeholders were not consulted on the possible amendments of horizontal aspects such as designation and monitoring of Notified Bodies, vigilance, market surveillance, need for further centralisation etc. which are currently under discussion in the framework of the recast of Directives 90/385/EEC and 93/42/EEC. These amendments would apply, *mutatis mutandis*, also to the revision of the IVD Directive.

Stakeholders were invited to submit their comments by 15th September 2010. Several comments received beyond the date were still taken into account. Altogether, the Commission received 183 responses. The repartition of answers by categories of stakeholders is indicated below. Mainly, answers were received from users (clinical laboratory associations, medical associations, hospitals and healthcare professionals) with 69 responses, from associations and laboratories active in the field of genetics (44 answers), from manufacturers and industry association (32 answers), from Competent Authorities (17 answers) and from Notified Bodies (13 answers).

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

As the questionnaire included a broad range of questions which were not of interest for all the stakeholders, the majority of the answers are only partial answers.

Among the 183 responses, 21 specified that the submission should be treated as confidential. The other answers are published together with this summary on the Commission website[2],



II. General Comments

The main message received though this consultation was that the revision of the IVD Directive is welcomed by the stakeholders, which was a confirmation of the feedback received from the previous public consultation.

The main highlights from this public consultation were that there is a broad support for the adoption of a risk-based classification. The second area where a broad consensus emerged was the need to keep an exemption for "in-house" testing. While some clarification would be needed, it was underlined in this public consultation as a major issue for clinical laboratories and users, especially in the field of genetic diseases.

The users (healthcare professionals, clinical laboratories) mainly provided answers only to the specific question regarding "in-house" tests, which was their main focus within this public consultation. Therefore to improve the reading of the results, the statistics presented for the analysis of the answers will be performed for each question based on the number of answers received to this specific question.

[2] http://ec.europa.eu/consumers/sectors/medical-devices/index_en.htm

III. Comments on specific items of the 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?*

The answers provided in the context of this public consultation confirmed the quasi unanimous support from stakeholders regarding the adoption of a risk based classification, which was already highlighted in the 2008 public consultation.

Among the 116 answers received, nearly 93% agreed on the fact that the adoption of a risk-based classification based on the Global Harmonisation Task Force (GHTF) model[3], would have a positive impact in terms of flexibility, allowing for a better protection of public health while being able to ensure a timely access to the market for new tests. In addition, the regulatory framework would become more robust to the technological progress.

Few economic data were provided during this public consultation. However it was underlined by some stakeholders that this alignment would increase the costs for the regulatory requirements, as the risk-based classification based on the GHTF model would require more frequently the involvement of notified bodies for the conformity assessment procedures, in particular for Class B and C tests. The majority of the respondents argued that this would increase costs for manufacturers significantly and finally underlined that these additional costs might be paid by the end users.

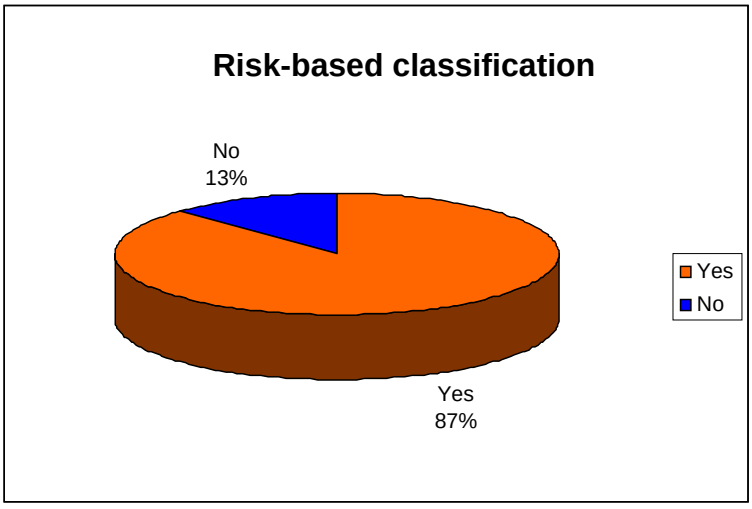
But the same stakeholders also pointed out that these increased costs should be balanced with the improvement of safety for public health brought by the implementation of more stringent regulatory requirements for some categories of tests. The issue of the higher costs might be addressed by allowing manufacturers a sufficient transitional period. According to the manufacturers, a sufficient transitional period (5 years) would avoid a

[3] GHTF/SG1/N045:2008 regarding Principles of In Vitro Diagnostic (IVD) Medical Devices Classification - http://www.ghtf.org/documents/sg1/sg1final_n045.pdf.

disproportionate impact on SMEs and on manufacturers without lowering the benefits of the adoption of a risk based classification.
Additionally, some submissions pointed out that the adoption of a risk-based classification, provided that it would be based on the GHTF model, would facilitate the exports for European manufacturers and would have therefore a very positive impact on competitiveness. Manufacturers underlined that the adoption of a risk based classification not based on the GHTF model would represent additional costs which would not be balanced against any financial benefit.

Another issue raised by some stakeholders was the fact that the risk based classification has to be detailed enough to avoid any controversial or inconsistent implementation. It was pointed out that any inconsistent application of the risk-based classification would lead to discrepancies and fragmentation within the internal market.
Other respondents underlined that the adoption of such a risk based classification should be implemented at the same time as appropriate guidelines or should be followed by the creation of an efficient and rapid mechanism to solve borderline and classification issues at EU level.

Some answers in the field of genetic testing raised concerns about the appropriateness of the GHTF model risk-based classification to genetic tests. These respondents suggested that this classification for genetic tests should take into account the impact of the potential test results on the patient and their family, as well as the likelihood of tests being performed and interpreted correctly, especially by lay users, the risk of incorrect measurement, the purpose for which the test is used and the potential consequences of error in the measurement.

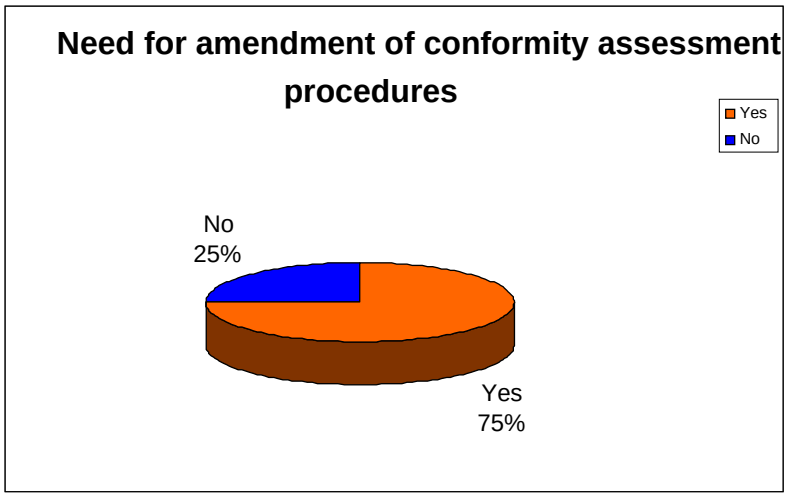


2. Conformity assessment procedure

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?*

108 answers to this specific question were received. Among these answers, 75% underlined that an amendment of the current conformity assessment procedure would be necessary.



The analysis of the respondents by categories showed that the highest percentage of positive responds came from Competent Authorities, Notified Bodies and manufacturers.

The following question, asked the respondents to provide some details about the conformity assessment procedures to be amended.

Question 3:

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

A majority of stakeholders underlined that Annex VI should be deleted, as this conformity assessment procedure is rarely used and does not include an assessment of the vigilance system, or should be limited to specific products like IVD instruments. Few respondents suggested keeping a wide range of possibilities in the conformity assessment procedures.

Many stakeholders underlined the need to align the conformity assessment procedure with the GHTF model.

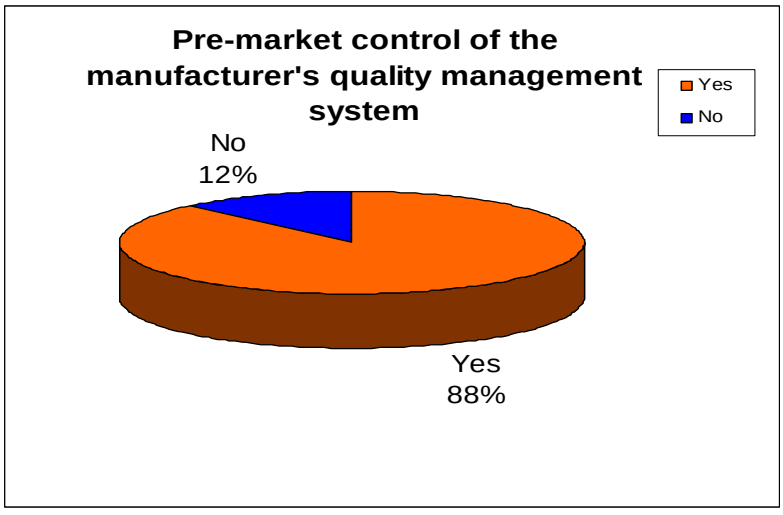
Some respondents identified that the adoption of a risk-based classification system based on the GHTF model will lead to major amendments regarding the conformity assessment procedure to be applied for self-tests. These self-tests will not fall under a particular category within the GHTF classification and therefore will not be classified differently from the same test to be used by healthcare professionals. This will lead to a major change as self-tests have specific requirements regarding the conformity assessment procedure to be applied according to the current Directive. Many answers, in particular from Notified Bodies, suggested deleting the possibility to perform a conformity assessment procedure according to Annex III.6[4] for self-tests, and underlined the need to align the conformity assessment procedures for self-tests to those applied for Annex II List B tests (e.g. tests for the detection and quantification in human samples of rubella, toxoplasmosis…) .

Other stakeholders mentioned the need to clarify the requirements set up in Annex V (Type examination).

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?*

82 answers were received to this specific question. Among these answers, 72 were positive, representing 88% of positive answers.



[4] Annex III (EC Declaration of conformity) point 6 foresees that for devices for self-testing the manufacturer shall lodge an application for examination of the design with a notified body.

Most of the respondents confirmed that a Quality Management System (QMS) should be put in place for Class B, C and D IVD medical devices according to the GHTF model and that this QMS should be controlled by a third party, as laid down in the GHTF documents. In addition some respondents underlined that the requirements on the QMS should be extended also to class A IVD medical devices.
However some stakeholders pointed out that even if such a QMS system controlled by a third party would be necessary, this would not be sufficient alone to ensure the safety of the products.

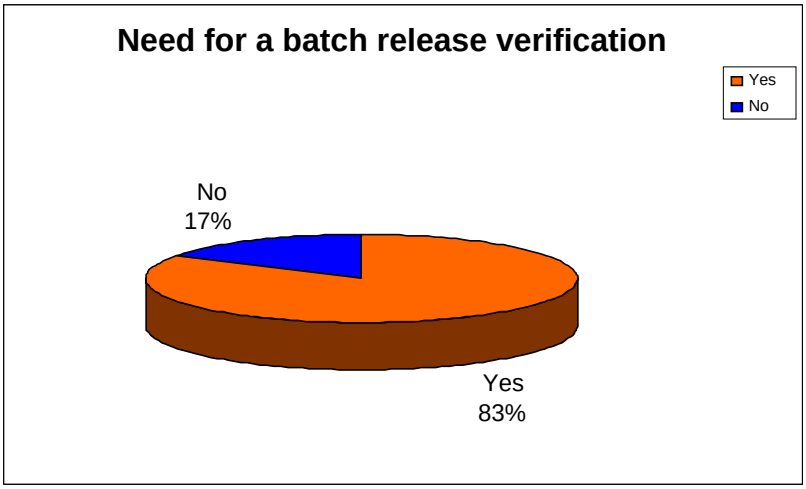
Question 5:

*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?*

115 answers were received. Among these answers, 83% considered that there is a need to have a batch release testing for high-risks IVD.



According to the respondents, the purpose of this batch release testing would be to ensure consistency between batches and a uniform level of quality for high-risk tests. Other stakeholders underlined that the purpose of this verification is also to ensure compliance of each batch of a high-risk IVD medical device with the Common Technical Specifications set up for tests listed in Annex II List A of Directive 98/79/EC. Other answers stated that the purpose of the batch release verification is to provide

independent evidence that the sensitivity, specificity and quality of each batch of an IVD medical device are acceptable when compared to the original approved assay for the purpose of the granting the CE marking. Few respondents underlined that this batch release testing performed before the placing on the market of the tests precludes low quality batches of high-risks tests to be placed on the market.

However, if a majority of respondents agree on the general purpose and the benefits of the batch release testing, there are some divergent opinions on how and by whom this batch release verification should be performed. A large amount of answers pointed out that this verification should be performed by the manufacturer, and must be part of the Quality Control and Quality Management System of the manufacturer, under the control of the Notified Bodies. This control could be based on a systematic verification or be subject to periodic inspection by the Notified Body. These respondents also pointed out that the methods, the reference materials and the panels used for this batch release testing should be approved and controlled by the Notified Body.

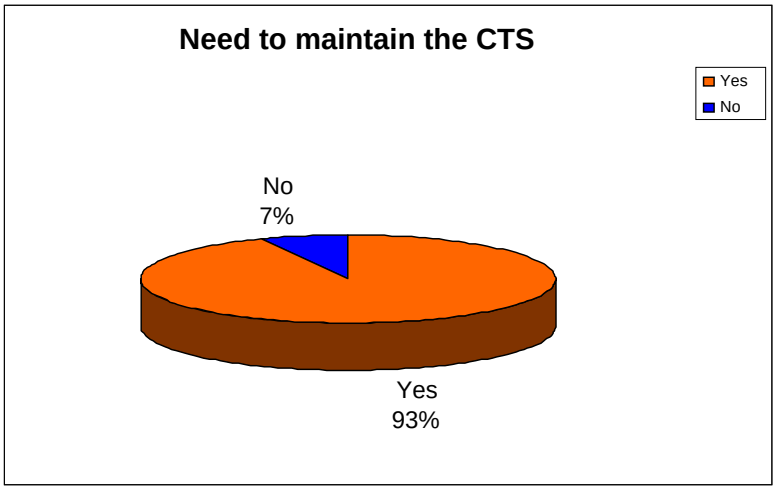
Some answers underlined the need for a batch release testing to be performed by an independent laboratory or by the Notified Body. However, other answers pointed out that the batch release testing performed by an independent laboratory would be too costly and would not bring an added value in terms of safety and quality.

However, the answers from manufacturers underlined quasi-unanimously that an internal batch release testing is already performed by manufacturers as an integral part of their Quality Management System, under the supervision of the Notified Bodies for high-risk products. They pointed out in their replies that a batch release testing performed by independent laboratories would be a duplicate of the manufacturer testing. Furthermore, they suggested that the batch release testing should be performed by the manufacturer and that the procedure to be used for the batch release testing, including the reference methods and the panels to be tested should be validated by the Notified Body. The notified body would then verify the results of this batch testing.

Question 6:

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

101 answers to this specific question were received. Among these answers, 92% underlined the need to maintain the CTS at least for tests used in the context of blood transfusion and/or for Class D tests, according the GHTF classification.



Although the majority of the respondents were in favour of not extending the CTS to other IVD tests, few answers stated that it might be beneficial to extend the CTS to tests within the Class C IVD medical devices according to the GHTF model.
Among the answers received, the Notified Bodies unanimously pointed out the need to keep the CTS.

3. Scope

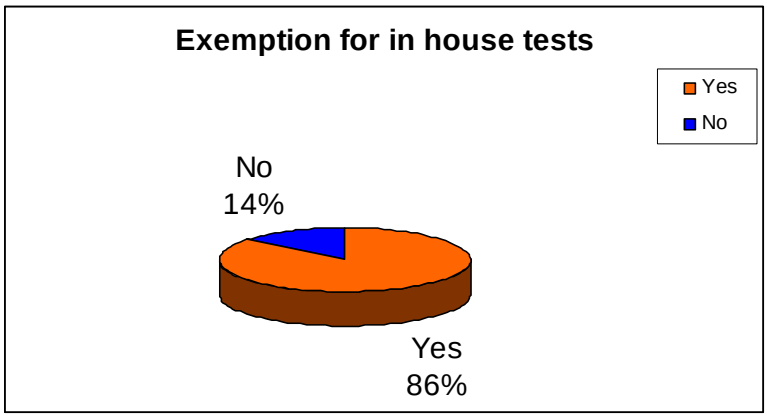
3.1 *Specific exemption for "in-house tests"*

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”.

The question is 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?*



144 answers were received.

According to 86% of the respondents the exemption provided in Article 1(5) of Directive 98/79/EC should be kept. In particular some respondents pointed out to some specific situations where the availability of in house tests is necessary. Examples given were for instance for novel analytes, rare disease testing, customized tests for common genetic diseases and population-specific tests and test panels. According to those respondents, the abolition of the exemption would result in the lack of availability of some specific testing and would be detrimental to patients. Another reason pointed out by the respondents for maintaining the exemption was the need for rapid response to changes in test requirements. Reference was made in the contributions to the recent years' rapid emergence of global health threats from infectious agents (e.g. SARS, Influenza H5N1, H1N1). Such outbreaks require the rapid development and deployment of new assays for detection, monitoring and vaccine development and, according to these respondents, it would not be possible to implement such testing in the time-scale required if each new assay had to go through the CE marking process. Contributions also pointed to the economic consequences on healthcare systems as well as to the consequences on research and innovation of an abolition of the exemption provided by Article 1(5) of Directive 98/79/EC.

However, in order to prevent unfair competition between CE marked in vitro diagnostic medical devices and in-house tests, various contributions pointed to the need of better defining the exemption and restricting it to situations were there is no similar commercially IVD devices available or where the commercially available IVD devices does not address the needs of the users with regard to the performances or to the intended purpose of the devices. Other contributions suggested that the exemptions should only apply to low risk, low volume tests and that all high risk tests should be subject to the same standards and level of scrutiny. Some respondents were of the opinion that similar conditions as for custom made medical devices shall be established instead of the current exemption. Finally some respondents considered that any allowed exemption for in-house tests should be specific and kept within strict limits *e.g.* taking into consideration the need for devices for detection of rare parameters, and not be based on just the aspects of being in-house manufacture. These

respondents suggested therefore removing the exemption for in-house tests and replacing it by a specific regulation.

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.*

With regards to **item 1**, while some respondents were of the opinion that it is more appropriate for the national Competent Authority to continue to provide any further guidance required on these definitions and that the Directive itself does not need to be more prescriptive. 92 contributors were in favour of introducing some clarifications in the concepts of "in-house test", "health institution", "premises of a manufacture or premises in the immediate vicinity" in order to ensure a better implementation of this provision. To the notion of "in-house tests" was sometime preferred the notion of "home brew tests" or "Laboratory Developed Tests (LDTs)". While some respondents were in favour of clarifying the concept of "premises in the immediate vicinity" to address for instance the issue of networks of public service laboratories with shared governance structure, some contributors suggested deleting this geographical concept. Only a few respondents provided with proposals for definitions but some contributors pointed out to the risk of narrowing too much the exemption and to the difficulty of producing definitions that would be acceptable and applicable in all Member States. Some contributors suggested limiting the exemption to public-sector health institution laboratories which are under the regulatory supervision of the national authorities and

distinguishing between commercial and non-commercial ventures. On the contrary a few contributions were against any proposition that an exemption should be confined to public health laboratories.

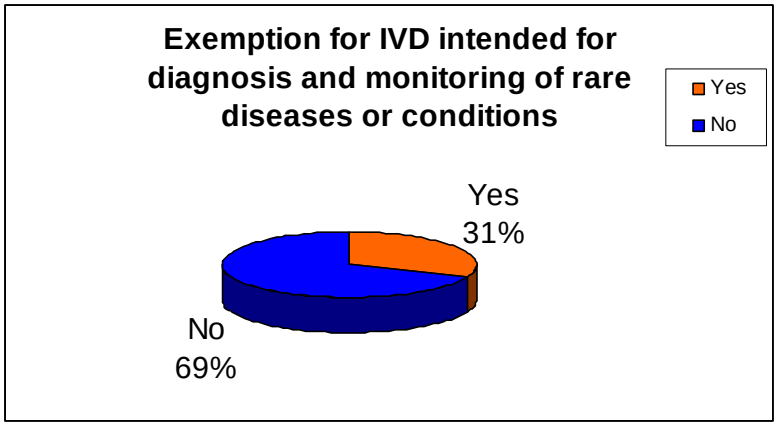
Items 2 and 3 were less supported by the respondents with respectively 41 and 27 supportive answers. In particular, for the item 2, respondents pointed out to the burden of compliance equivalent to that imposed by CE-marking. Some respondents suggested introducing some minimal provisions such as the inclusion of in house tests into the vigilance system, the registration of in house tests and, for in house tests in class D, the compliance with CTS and applicable essential requirements.

The proposal made in **item 4,** *i.e.* to 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, was supported by 81 contributors. Extensive reference was also made to ISO 13485 and ISO 17025. Some respondents suggested **combining items 3 and 4,** including high risk devices falling in both Class D and Class C.

***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?*

108 answers were received.



The proposal to exempt in vitro diagnostic medical devices intended for diagnosis and monitoring of rare diseases or conditions as defined above was not supported by 69% of the respondents.

Contributors pointed out to some difficulties in this approach such as cases where there is no commercially available test for infrequent but not rare conditions, cases where there is no commercially available test for a specific condition e.g. newly identified condition and cases where conditions may be different in the Member States.

3.2 *Genetic test*

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.** However the medical purpose might not be so clear for some other tests like predictive tests or lifestyle tests, and may lead to different interpretation on the qualification of these products within the European Union.

***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?*

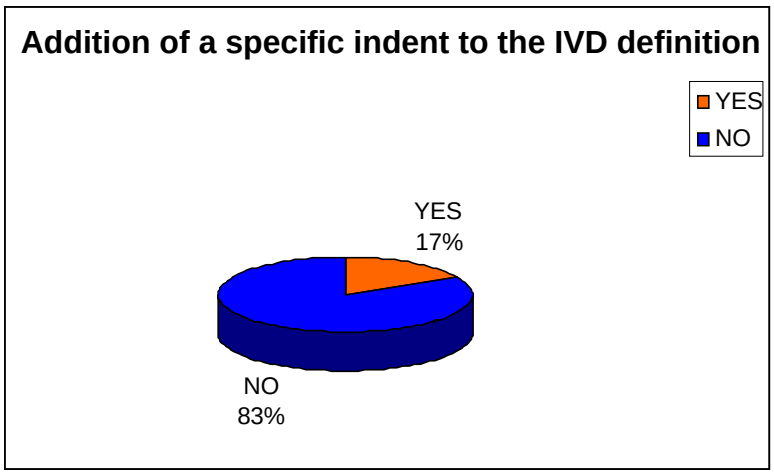
Item 2:

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

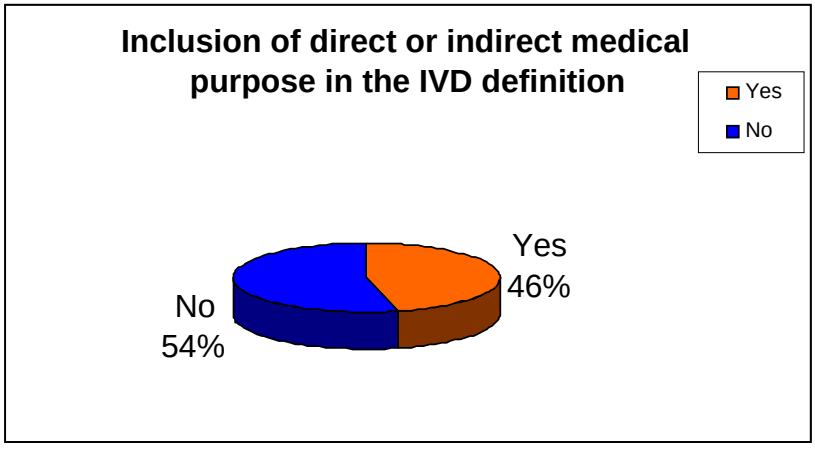
The contributors were asked to choose between two items.

The **item 1** was to enlarge the scope by including "results obtained by analysis of the genome" in the definition of *in vitro* diagnostic medical devices, and by introducing a negative list of some categories of genetic tests. This idea was judged as inappropriate by 83% of the respondents arguing for instance that the proposed additional indent in the definition of in vitro diagnostic medical devices is not broad enough to cover for example some tests based on analysis of RNA, protein or other (combinations of) biomarkers. The suggested wording could leave the status of such tests unclear.

In addition a negative list would be, according to some respondents, difficult to update and to be comprehensive and precise enough.

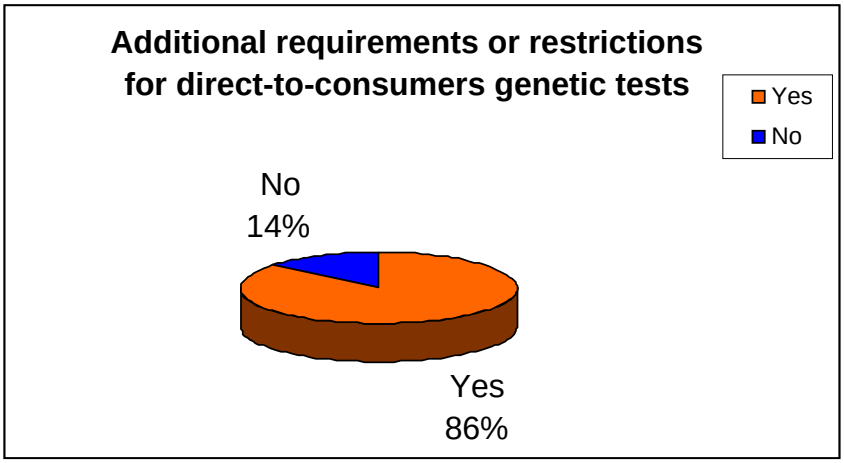


The **item 2** suggested the inclusion of "*direct or indirect medical purpose*" in the *in vitro* diagnostic medical devices definition.
This proposal was not supported by 54% of the contributions. Among those who were in favour of this option, the need of a clear definition of what is a direct and indirect medical purpose was pointed out in several answers. Some contributors were of the opinion that the addition of the word “prediction” to the definition of a medical device in Article 1(2)(a) might help addressing the issue, and in particular the uncertainty around certain tests with a (claimed) predictive value. Some contributors were of the opinion that such clarification should be made in a MEDDEV and not in the Directive itself.



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?*



80 answers were received.

86% of the respondents agreed that additional requirements or restrictions for direct-to-consumer genetic tests should be created to ensure a better level of health protection. Appropriate medical intervention and counselling were mentioned as important aspects to be addressed. Some contributors were of the opinion that the same requirements as those currently requested for self-testing devices should apply.
Some respondents pointed out to the need to ban the direct sale to the public of genetic tests and advertising directly targeting the general public. According to these respondents the genetic tests for health purposes must be carried out by qualified staff in centres accredited by the health authorities. Extensive reference was made to the OECD guidelines on quality assurance for molecular genetic testing.

3.3 *Diagnostic services*

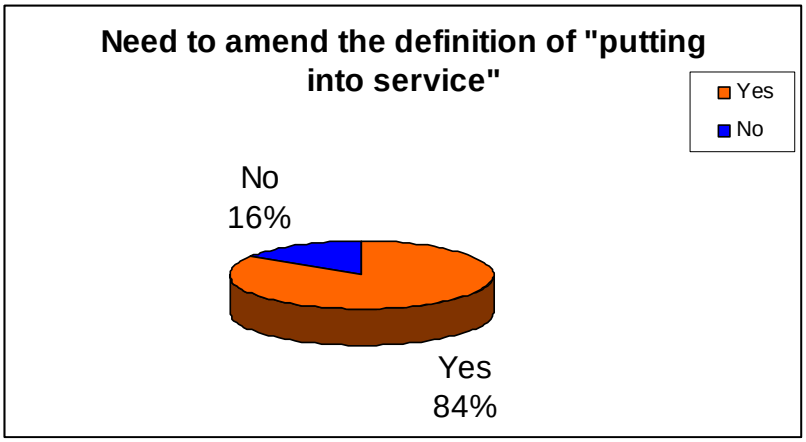
There are an increasing number of tests which are performed within an economic operator's facility (within the EU or outside) **without placing the *in vitro* diagnostic medical devices on the market**. Despite Recital 11 and Article 9(13) of Directive 98/79/EC[5] it may not always be clear that IVD's used in such a situation are subject to Directive 98/79/EC. There are **increasing concerns** regarding the validity and the

[5] 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."

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?*



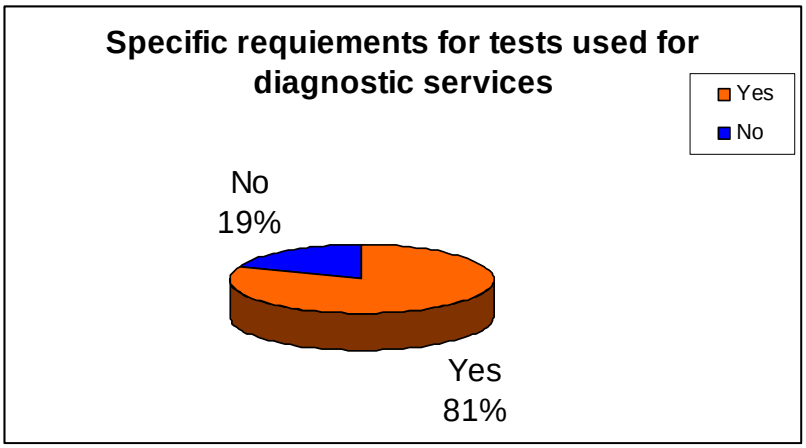
76 answers were received.

Reference was made to Recital 11 and Article 9(13) of Directive 98/79/EC but for the sake of clarity the need to amend the "putting into service" definition was supported by 84% of the respondents. While acknowledging possible difficulties in the implementation, those respondents were of the opinion that the definition of 'putting into service' should also be applicable to diagnostic services, including the diagnostic services which are performed outside the EU, and of which the test result are communicated inside the EU

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?*

74 answers were received.
81% of the respondents were in favour of introducing specific requirements for tests used for diagnostic services, especially when the results of the tests are provided directly to consumers.



Examples of additional requirements mentioned were requirements for marketing and advertising (for instance CE-mark and Notified Body number mentioned in the advertising), establishment of standard operation procedures, procedures for incident notification and patient information, involvement of healthcare professionals in the delivery or redaction of the results delivered directly to the consumer. The respondents highlighted the importance that the information transmitted to the consumer is comprehensible, objective and not misleading while providing sufficient explanations, for instance with regard to the achieved quality of test results and the limits of validity of the method and with the need for further advice or consultation through a healthcare professional where needed. Information on the institution offering the testing service, such as for instance information on its accreditation, was mentioned by some contributors. Some respondents pointed out to the difficulties of enforcement of certain of these requirements. Extensive reference was made to the Human Genetics Commission's report A "Common Framework of Principles for direct-to-consumer genetic testing services"[6] . Some contributors pointed out that the issue of advertising should be addressed in the context of all three medical devices Directives.

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[7].

[6] http://www.hgc.gov.uk

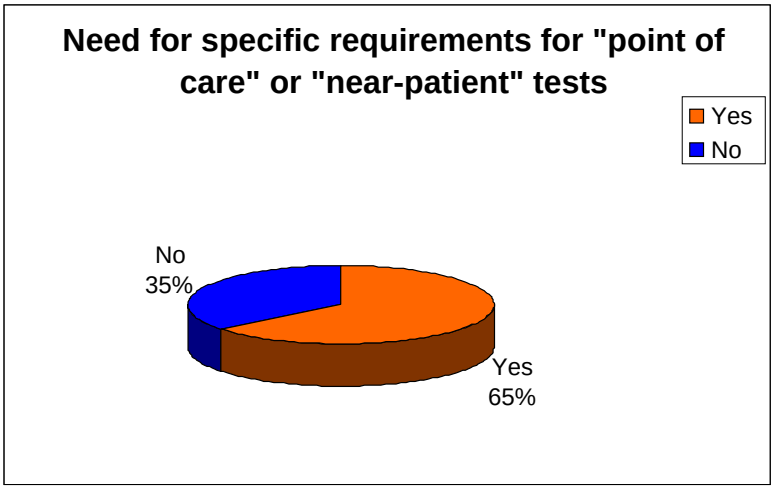
[7] GHTF/SG1/N045:2008 regarding Principles of In Vitro Diagnostic (IVD) Medical Devices Classification (see above footnote 6) defines "near-patient testing" as "testing performed outside a laboratory environment by a healthcare professional not necessarily a laboratory professional, generally near to, 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)?*

93 answers were received.

Among these answers, 60 answers (65%) underlined the need to set up specific requirements for point of care or near-patient testing.



Few respondents pointed out that the current requirements in the Directive already address this issue as the intended user must be taken into account for the CE marking. However most of the respondents underlined that the current requirements are not sufficient. They suggested that the clinical validity of the test must be demonstrated in the same conditions than those in which the test will be used. According to the respondents, the manufacturer shall demonstrate that the tests performed in a point of care environment provide the same level of clinical sensitivity or specificity than the test performed in a clinical laboratory. In addition, it was underlined that these tests and the users of these tests should be subject also to a Quality Management System, including Quality Controls, maintenance and External Quality Evaluation schemes, as well as to an appropriate training to the use of these tests.

Few respondents underlined that a diagnosis should not be performed on the basis solely of such a test and that the results should be confirmed by a clinical laboratory.

Other aspects raised by many respondents were the need to add some specific requirements regarding the handling of these tests by healthcare professionals as well as the need to have the instructions for use understandable by lay person. The aim of the additional requirements would be to avoid any possible misleading tests or inappropriate interpretation of the results. Specifically, the need to have a clear and appropriate explanation on the meaning of the diagnosis sensitivity and the diagnosis

specificity as well as on the negative and positive predictive values was underlined by a majority of respondents.
Some respondents pointed out that the IVD Directive should exclude the possibility to perform in house tests in a point of care environment, due to the lack of appropriate instruction for use.
In addition, few respondents underlined that genetic testing should not be performed in a point-of care environment, due to the need to have appropriate information for patients.

4. Clinical evidence

The respondents were asked to answer on the need to clarify the requirements regarding the clinical evidence. The stakeholders were also consulted on the need to extend the requirements regarding the clinical utility and on the need to set up requirements on the clinical utility.

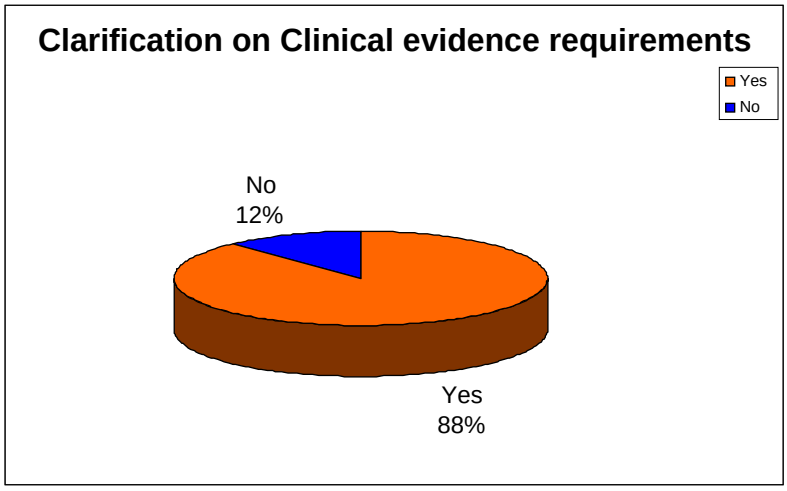
Question 15:

*Do you see a need to **further clarify the requirements regarding clinical evidence** for in vitro diagnostic medical devices?*[8]

110 answers were received.

Among the answers, around 90% of the respondents agree on the fact that the requirements regarding the demonstration of performance for IVD medical devices need to be clarified. For the majority of the stakeholders, the current requirements on the demonstration of performance set up in the IVD directive are misleading and may be interpreted as being only analytical requirements.

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



In addition, the respondents agreed that the requirements regarding the clinical evidence should be more detailed in the Directive and that the Directive should include some requirements on how to demonstrate the clinical evidence.
A suggestion made by the stakeholders was to better align the requirements on clinical evidence for IVD medical devices on those required for medical devices, by introducing a specific Annex on the requirements on clinical evidence, aligned on Annex X of the Directive 93/42/EEC.
A majority of stakeholders also pointed out that the level of requirements regarding the demonstration of clinical evidence should be adapted to the different classes of the IVD medical devices.
Mainly a quasi unanimous opinion on the need of clarification of clinical evidence was expressed by the Notified Bodies and by the stakeholders in the field of genetic testing. Among the users and Competent Authorities, more than 80% of the answers underlined the need to clarify the requirements on clinical evidence.

The next questions are related to the proposition to clarify the requirements on clinical evidence in the Directive in the light of the on going work at GHTF level on the demonstration of clinical evidence for IVD medical devices and to the introduction the concept of clinical validity in the Directive.

4.1 *Clinical validity*

The **clinical validity**[9] was defined within the public consultation as 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

[9] 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

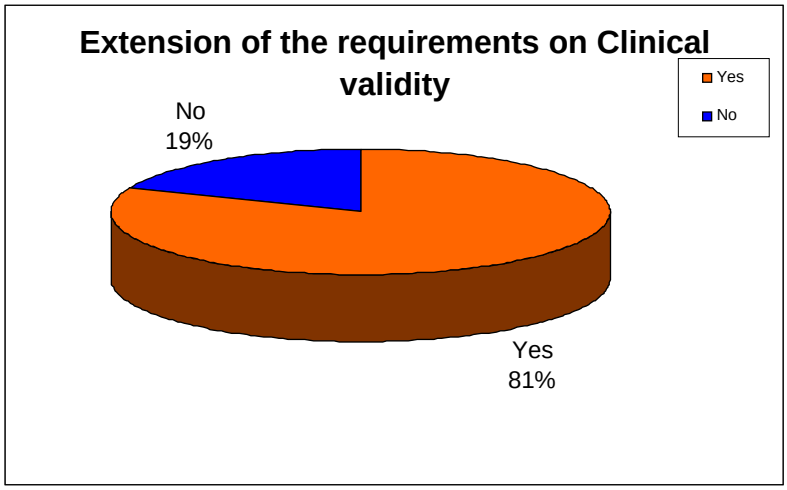
true disease status of the patient and negative and positive predictive values based on the prevalence of the disease. These two last elements (negative and positive predictive values based on the prevalence of the disease) are currently not clearly mentioned in the Directive 98/79/EC.

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?*

106 answers were received.

Among these answers, 81% expressed some support for extending the requirements in the Directive to the demonstration of the clinical validity for IVD medical devices.



The stakeholders agreed quasi unanimously on the fact that the requirements on the demonstration of the clinical validity should be extended at least to the demonstration of Negative Predictive Value and Positive Predictive Value. Among the respondents, there was a large support to this proposition from Competent Authorities, Notified Bodies and users. Among manufacturers there was little support to this proposition.

Mainly the stakeholders pointed out that the requirements on clinical validity should be proportionate to the risk linked to the use of the IVD medical device and then adapted to the risk based classification.

It was underlined by few respondents that the compliance with the Common Technical Specification should be considered as part of the demonstration of the clinical validity and then that their use should be expanded to other IVD medical devices. This answer is however in contradiction with the answers provided to question 6 where a large majority of stakeholders expressed the view that the CTS should not be extended to non high- risk IVD medical devices.

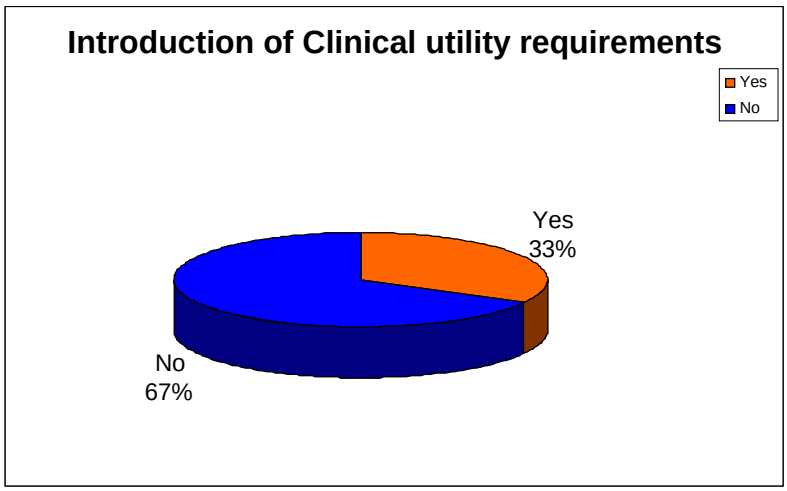
4.2 *Clinical utility*

For the purpose of this public consultation, the notion of **clinical utility**[10] was defined as 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?*

Regarding the concept of clinical utility, the question raised was the need to define the clinical utility within the legal framework, according to the definition provided above and to require its demonstration by the manufacturer as a part of the conformity assessment process.
115 answers to this specific question were provided. The majority of the respondents (67%) expressed a negative opinion on the need for the demonstration of the clinical utility by the manufacturer.



Mainly, the concerns raised were that the concept of clinical utility is a moving concept that might hardly be addressed in the regulatory framework. In addition, a lot of

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

respondents underlined that the concept of clinical utility should remain outside of the pre-market assessment process.
In addition, it was underlined that the clinical utility should not be demonstrated by the manufacturer, but should be assessed by the user. The user would have to decide on the clinical utility of a specific IVD medical device in a specific context or a specific population. Among the respondents, manufacturers, Notified Bodies and stakeholders active in the field of genetics were against introducing requirements on clinical utility within the Directive. Even users were not favourable to the introduction of such requirements in the Directive.

It was underlined that for new parameters, it will be impossible to demonstrate the clinical utility and therefore, it will limit the market access for innovative IVD medical devices. At the same time, some stakeholders underlined that for the majority of well known parameters, the demonstration of clinical utility should not be required.

However, some of the answers underlined that the demonstration of clinical utility might have an interest for direct to consumers testing or genetic testing.

5. Others

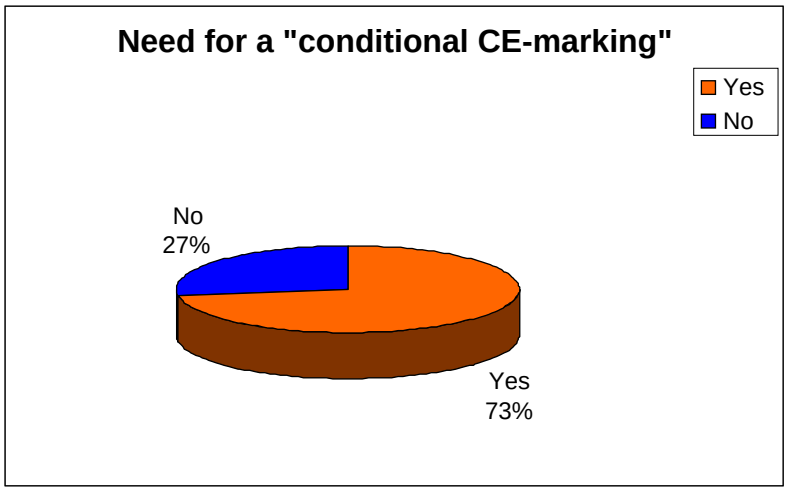
5.1 *"Conditional CE marking"*

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?*

The stakeholders provided 117 answers to this question. A majority of them (73%) considered that a "conditional CE marking" might be a useful in certain situation.



The respondents raised some questions regarding this "conditional CE marking", in particular regarding the aspect of who would decide to allow such a "conditional CE marking". There is a fear that this "conditional CE marking" would allow the marketing of low quality tests. Some answers underlined that if such a procedure would be put in place, a committee composed of Competent Authorities' representatives should be responsible for the decision.

It was underlined by the stakeholders that article 9(12) of Directive 98/79/EC already address the emergency situation on a national basis. A majority of Competent Authorities pointed out that they would prefer to keep this "derogation" at national level. It was underlined by the other categories of respondents that it would be useful to have such a "conditional CE marking" at European level to address the emergency, like a pandemic, as the situation of a pandemic would rarely be limited to a Member State.

The broad majority of respondents pointed out that the situations in which such a procedure would be useful are the emergency, (*i.e.* spread of a new disease, pandemics,..) or the timely access of tests for unmet medical needs.. In that case, the test would be subject to a post-marketing collection of data and then to a CE marking on the basis of the data collected.

However it was underlined by the stakeholders that this procedure would not be useful for "rare conditions". It was pointed out that in the case of "rare conditions", the more efficient procedure would be an exemption from the IVD Directive, as mainly these tests are performed in an in-house environment and it is very unlikely that sufficient data might be collected to obtain the CE marking.

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 respondents provided 125 answers to this question.

Almost unanimously, the respondents underlined that the IVD medical devices used as companion diagnostics must be subject to the IVD Directive, which will ensure an appropriate level of quality and safety for European citizens. The respondents pointed out that the implementation of a risk-based classification would address the main concerns raised about the insufficient level of scrutiny for these IVD medical devices. It would be necessary to have these IVD medical devices in Class C of the GHTF model, to ensure that a third party would be involved in the CE marking of these devices. However some respondents pointed out the need to have a closer cooperation between IVD medical device sector and the European Medicine Agency.

Some respondents underlined the need to require for these IVD tests the demonstration of the clinical utility of the combination of the medicinal product and the IVD medical device in the context of the CE marking and the marketing authorisation of the medicinal product.

It was underlined by stakeholders in the field of genetic diseases that the competence of the European Medicine Agency should be extended to pharmacogenomics, as the IVD medical device has an impact on the health outcome of the medicinal product and then the analytical and clinical validity of the IVD medical device should be part of the assessment of the benefit/risk assessment of the medicinal product.