Dear sirs,

Please accept this response to the public consultation.

This response is submitted on behalf of the ‘Notified Body – IVD – Working Group’.

This group is set up as a working body as part of the ‘Notified Body Recommendations Group’ and hence reports up through NBRG to NB-MED, and is open to trade associations and Notified Bodies.

Yours sincerely

John Andrews
Chair of NB- IVD- Working Group.
**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?

Yes, a risk based classification system is considered to be an improvement to a list based system as it will be more flexible to cope with challenges resulting from ongoing technological or diagnostic progress. I.e. a well constructed set of rules should result in less frequent needs to revise the legal text (compared to a list based system) as it should provide the ability to classify new products, not yet considered.

However we could anticipate that a rule based classification system may lead to more frequent problems in interpretation compared to a strictly defined list based approach. Therefore to ensure consistency in interpretation of classification rules a guidance paper (preferably a MEDDEV document) providing more examples for classification especially for class B would be considered as necessary.

Note: the rules as currently written in GHTF/SG1/N045:2008 would not be considered precise enough to achieve the benefits as above because they appear to be open to interpretation.

- Are you aware of any consequences for the protection of public health?

If the final adoption of risk based rules only achieve a requirement for third party conformity assessment for the same device types as current then obviously no benefit will arise.

However a change to classification that increases the input of third party conformity assessment either for the quality system or quality system and product will potentially improve the protection of public health.

And if uniformity of assessment methodology is also incorporated i.e. linking notified body technical documentation sampling to classification as introduced by the Medical devices Directive 2007/47/EC then the change should result in further improvements.

No negative impact is considered.

- Can you provide economic data linked to a change-over to this GHTF classification system?
It is anticipated that there will be some increase in costs to manufacturers.
Additional costs to manufacturers would arise if the number of device types requiring third party conformity assessment is increased as a result of a change to classification rules and/or if technical documentation sampling rules for Notified Bodies were adopted.
There could be a potential for increase of costs for Notified Bodies due to additional qualification efforts to cover products not yet considered by the Directive which would need to be offset by increase of costs to manufacturers.

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?

Yes, we consider a “GHTF type” risk based classification system should be applied which would require guidance on (rules for application by device type) implementation of conformity assessment procedures.

Note: the current conformity modules may not require amendment, it is the rules defining which module/combination of modules is applicable to any given defined device class that would require elaboration.

For example using the GHTF model as current one would anticipate: Class D - same conformity assessment procedures as currently applied for Annex II, List A products. Class C - same conformity assessment as currently for Annex II, List B products.

For Class B, which would be considered new compared to the existing Directive it is anticipated that conformity assessment modules similar to applicable conformity assessment procedures for class IIa products under Directive 93/42/EEC would be defined.

Class A: self declaration of conformity by the manufacturer.

In addition it would be anticipated (welcomed) that sampling rules of technical documentation would be introduced as per the amendment of 93/42/EEC by 2007/47/EC and that this would be analogous to the principles in NBOG 2009-4.

Question 3:

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

We are aware that other respondents have advocated deletion of Annex III point 6 for self test devices. Unless market surveillance data is available showing that this option does not provide the required level of protection of public health we would advocate maintaining it as an option. Otherwise such devices would need to be identified in one of the risk based classification sets and relevant conformity procedures applied to require NB involvement.
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?

We consider that for all manufacturing activities related to reagents that would (depending on any risk based system adopted) be equivalent to reagents of GHTF Classes B to D, an assessment of the quality system of the manufacturer by a third party should be performed.

However we consider that in the framework of the new approach this should be by designating quality system assessment as part of the requirement for conformity assessment and not by adding third party quality system assessment as an additional requirement on top of prescribed conformity assessment modules.

The third party assessment therefore would be ‘only’ by a designated Notified Body in performance of a conformity assessment module.

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?

Yes we consider that control of each batch of manufactured high risk IVD’s prior to their placing on the market should be retained.

And that this should be maintained for devices that, irrespective of any new classification system, would currently be defined under Annex II List A, screening assays.

We would promote the creation of a MEDDEV guidance to describe verification of manufactured product requirements including different modalities e.g. independent physical testing, testing of unknown samples, witness testing, including requirements for qualification of test laboratories, options to reduce physical testing following good product history.

Question 6:

Should the use of Common Technical Specifications (CTS) be maintained for high-risk IVDs? Should CTS also be adopted for other IVDs?
Yes – in our experience the application of Common Technical Specification (CTS) has been reasonable and practical and should be kept (and if necessary, extended) for all high risk in-vitro diagnostic devices.
There would be merit in extending the scope to other risk class devices if no performance related harmonised standards exist and provided a mechanism for not only the origination but also the regular review and revision of such CTS was provided for.

3. Scope

3.1 Specific exemption for “in-house tests”

Question 7:

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

We do not consider it appropriate to maintain the exemption in its current form.
Our concerns with the exemption in the current format are:

- There is no requirement for hospitals to make vigilance reports, hospitals (any exempted manufacturers) should be required to register and report vigilance cases in a similar way to the provisions of 93/42/EEC as amended by 2007/47/EC for custom made devices.
- In house testing is often conducted on a commercial scale, there should be consideration to the number of tests performed e.g. per annum, and the prevalence of the disease state in a similar way to how the MDD limits use of custom made devices, whilst an individual “prescription” would not be appropriate we consider that some criteria could be defined to limit the risk to the population.
- Hospitals have little, verified, experience of designing manufacturing processes to prevent batch to batch variation; for example process validation, stability studies etc. this would apply to both new assays and situations where hospitals have diluted reagents to increase the number of tests per kit. Although we recognise that hospitals often operate quality systems for delivery of a testing service, this does not typically address the GMP requirements of ISO 13485.
- We consider that there should be no exemption for high risk devices such as currently listed in Annex II List A or GHTF Class D.

We would consider 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.

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?

Yes (would require better definition) – If the concepts are to be embedded within the regulations and consequences arise from their application, to achieve consistency.

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 (any exempted) in house tests should meet applicable ER’s and be subject to design and manufacturing controls e.g. by operation of a quality management system. Exempted manufacturers should be required to register with a competent authority and meet vigilance requirements.

I.e should meet all the requirements designed to protect patient health, only exempt from third party review, still subject to market surveillance.

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 – we consider that high risk devices should be excluded from any “in house testing exemption” and should meet the requirements of the CTS.

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?

We do not consider that ISO 15189 addresses GMP requirements for consistent manufacture of IVDs.

We would expect healthcare institutions to meet the QMS requirements as described in the Directive.
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?

Yes - we can see a rationale for exemption for rare disease IVDs which should still provide for conformance with certain specified provisions but without economic penalty of third party intervention.

3.2 Genetic 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.

No – our main concern as notified bodies is the robust application of the directive, clear definitions are essential but our concern would be the definition of indirect. We suggest that the term indirect could give rise to more confusion, for example, does a nutrigenic test have an indirect medical effect because obesity will have a medical impact? If this definition is introduced guidance will be required to support implementation. It would be more appropriate to consider that genetic tests (as any test type) which meet the definition of an IVD are within the scope of the directive. If it is considered that additional regulation is needed for other types of genetic tests this should be covered by other, separate, legislation.

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?

No – this field is constantly evolving and any list of exclusions could become out of date within the lifetime of the directive, there should be criteria for inclusion not exclusion, based on the current definition of an IVD. If necessary guidance could be provided e.g. in a MEDDEV document.
**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.

No – this would confuse, however as indicated a MEDDEV document could provide additional interpretation guidance.

**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?

We suggest that direct-to-consumer tests (whether genetic or otherwise) could be interpreted as self testing devices and as such be subject to a third party review in the same way as self testing devices are currently regulated.

**3.3 Diagnostic services**

**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?

Yes – clarification would be required to ensure consistent application. Clarification could either be within the directive or in the form of Commission guidance.

**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?

No – we do not consider a need to add requirements related to advertising in a new approach directive, however we would expect notified bodies to review advertising in relation to product claims and performance characteristics.

Consideration should be given to requirements such as sample collection e.g. ability of the user to successfully collect and transport a viable sample.
3.4 Point-of-care / near-patient in vitro diagnostic medical devices

**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)?

| Yes - Currently the IVD Directive 98/79/EC defines two user groups: professional & lay users. IVD regulations in other markets (e.g. USA, Canada) and guidance documents (GHTF) define an additional group of products: near-patient or point of care tests used by a healthcare professional, not necessarily a laboratory professional e.g. nurses, pharmacists. The final assessment of the test result is not in all cases performed by a physician. *Therefore whilst specific requirements might not be considered necessary – we would expect that e.g. evaluation of the performance of the device should be conducted using subjects representative of the envisaged user(s).* |

### 4. Clinical evidence

**Question 15:**
Do you see a need to further clarify the requirements regarding clinical evidence for in vitro diagnostic medical devices?

| Yes – we consider it would be beneficial to have further defined requirements for clinical evidence, *proportionate to risk.* |

#### 4.1 Clinical validity

**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?

| Yes – the requirements should be extended either in the appropriate essential requirements or by improving harmonised standards for performance evaluation. |

#### 4.2 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?

No – we do not consider that demonstration of clinical utility should be required as part of performance evaluation of an IVD.

For established markers, clinical utility may be established from the literature, the big question is how much data would be required for novel markers, especially those used to provide additional data to support diagnosis or monitoring but not used in isolation.

The data required should be commensurate with the claims made for the test and the risk of the analyte.

For example more data would be required for a cancer marker used to screen a population where patients who test positive subsequently require a biopsy or invasive investigation compared to a marker used to support the diagnosis or monitoring of treatment and used in conjunction with other medical data.

A generic requirement for the same level of data for all types of tests would delay availability to the market.

5. Others

5.1 “Conditional CE marking”

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?

No – under the conditions listed (e.g. in case of a pandemic) an option for rapid market access of IVD devices is considered necessary and reasonable even if evidence required for regular conformity assessment may not be available. The option should however be restricted to well defined cases, for a limited period of time, with specific obligations on the manufacturer.

The approval to market access should be given by a Competent Authority on a European level.

As the respective devices have not fulfilled and been subject to conformity assessment they should not bear CE marking.
5.2. Companion in vitro diagnostic medical devices (e.g. pharmacogenomic assays, biomarker assays)

Question 19:

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

The level of oversight should be associated with the risk of the drug/diagnostic combination. For example if the test identified patients who would have severe life threatening complications if they took the drug then this should be high risk and require third party review. If the test optimised treatment but did not have severe consequences this would be a lower risk category. Classification and required assessment should be based on risk e.g. by application of “GHTF type” categories.