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PART III - Annex 2

COMMISSION STAFF WORKING DOCUMENT

IMPACT ASSESSMENT ON THE REVISION OF THE REGULATORY FRAMEWORK FOR MEDICAL DEVICES

Accompanying the documents

Proposals for a Regulation of the European Parliament and of the Council

on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009

and

on in vitro diagnostic medical devices

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1. PROBLEM DEFINITION

1.1. Problem IVD-1: Scope – regulatory gaps or uncertainties

1.1.1. "In-house" tests

Article 1(5) of the IVDD makes provision for an exemption for *in vitro* diagnostic medical "*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 usually called "in-house" tests. The concept of such tests has led to diverging, and sometimes very broad, interpretations in the different Member States. This exemption has come under criticism since it dos not ensure a uniform high level of safety and performances for "in-house" tests across Europe. Moreover, from the perspective of industrial manufacturers, the exemption from the requirements of the IVDD may lead, in certain cases, to unfair competition between CE marked IVDs and "in-house" tests. However, for certain medical conditions or in emergency situations, only "in-house" tests may be available. This requires therefore a careful assessment if there is a need to clarify or limit the scope of the exemption and/or to submit some or all "in-house" tests to certain requirements of Directive 98/79/EC.

1.1.2. Genetic tests

Currently, the IVDD only applies to genetic tests that have a medical purpose, e.g. prenatal diagnostic tests, diagnostic tests of diseases, tests used in conjunction with the use of a specific medicinal product, etc. Beside these tests with a direct medical purpose, the medical purpose cannot always be established for some predictive tests, lifestyle tests, nutrigenetic tests, etc. which provide information on the basis of the analysis of a human body sample. This might lead to different interpretations on the qualification of these products within the European Union. In addition, there are increasing concerns regarding genetic tests without a clear medical purpose (e.g. some predictive tests)[1]. These concerns are related, among others, to the lack of quality, of scientific evidence and of clinical validity or clinical utility of these tests.

1.1.3. Companion diagnostics in personalized medicines

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, etc. Currently, most companion diagnostics are self-certified by the IVD manufacturers. The increasing development of personalized medicines[2], and the close relationship between the companion diagnostics and the medicinal products, has raised the question whether a specific regulatory framework for companion diagnostics would be needed.

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1 European Technology Assessment Group, Direct to Consumer Genetic Testing, Nov. 2008; Süddeutsche Zeitung, 19.6.2009, "Blick ins Erbgut verwehrt"; Financial Times, 14.6.2010: "FDA in genetic test crackdown as clients are given wrong results"; Daily Mail, 31.5.2011: "Call to ban mail-order DNA disease testing kits that claims to predict life-threatening illnesses".

2 Clinica, March 2011, p.22-28, "Perfect companions" and "Improving the regulatory framework for companion diagnostics".

1.2. Problem IVD-2: Classification of IVDs and their appropriate conformity assessment, including batch release verification

The classification of IVDs according to the risk linked to their use, in particular in case of failure or misdiagnosis, is currently different from the approach taken for the other medical devices. The IVDD addresses the level of risk by listing "high-risk" IVDs (e.g. tests for the determination of blood groups and for the detection of HIV or hepatitis infection) in its Annex II. While this system gives a high level of legal certainty, it does not go along with technological evolution since the enumerative list needs to be adapted every time a new "high-risk" IVD is being developed. So far, the list has never been amended but the inclusion of assays for the detection of variant Creutzfeld-Jacob Disease is under way. However, the process is lengthy, and until any amendment of Annex II takes effect, new high-risk IVDs can be placed on the market under the manufacturer's self-certification.

The Global Harmonization Task Force (GHTF) adopted a guidance document GHTF/SG1/N045:2008 entitled "Principles of *in vitro* Diagnostic (IVD) Medical Devices Classification"[3]. Such rules-based risk classification is more robust to technological evolution. A majority of respondents to the 2008 and 2010 public consultations were in favor of the adoption of the GHTF classification which would replace the current Annex II of the IVDD.

The conformity assessment procedure that an IVD must follow before its placing on the market is directly linked to the IVD's risk class. If the GHTF classification was to be adopted, it would also be necessary to adapt the conformity assessment procedures to the new classification rules. The GHTF guidance document GHTF/SG1/N046:2008, entitled "Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices"[4], sets out the elements of conformity assessment applicable to the different classes of IVDs.

In addition, the IVDD requires a verification of manufactured IVDs listed in its Annex II, List A. This process is called "batch release verification". The testing of batches of high risk IVDs before their release shall ensure the consistency and the uniform level of quality of these tests, thus preventing low quality batches to be placed on the European market. However, the relevant provisions[5] have led to diverging interpretations and their implementation is not uniform in the EU which may lead to competitive disadvantages for certain manufacturers. While at least one Member State (Germany) requires systematic batch release verification to be performed by an independent laboratory, the batch release verification is performed by the manufacturer under the control of a Notified Body in other Member States.

1.3. Problem IVD-3: Unclear legal requirements and need for their adaptation to technological progress

1.3.1. Clinical evidence

The essential requirements of the IVDD contain requirements regarding the performances of IVDs. In particular, the demonstration of performances should include, where appropriate, the analytical sensitivity, diagnostic sensitivity, analytical specificity, diagnostic specificity, accuracy, repeatability, reproducibility, including control of known relevant interference, and

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3 http://www.ghtf.org/documents/sg1/sg1final_n045.pdf

4 http://www.ghtf.org/documents/sg1/sg1final_n046.pdf

5 Annex IV, section 6 and Annex VII, section 5 to the IVDD ("verification of manufactured products covered by Annex II, List A").

limits of detection, stated by the manufacturer[6]. These requirements are a mix of analytical and clinical performances requirements but are misunderstood as requiring only the demonstration of analytical performances. A vast majority of respondents to the 2010 public consultation were therefore in favor of clarifying the concept of demonstration of performances by introducing more detailed requirements on the clinical evidence required for an IVD in order to support the intended purpose, proportionate to the risk related to its use.

1.3.2. IVDs intended for point-of-care or near-patient testing

There are a growing number of tests which are performed outside a laboratory environment but near to a patient by a healthcare professional in order to make a diagnosis and/or to determine the appropriate treatment. These tests are often referred to as "point-of-care tests" or "near-patient tests"[7] (hereafter referred to as "PoC/NP-tests"). The benefit of PoC/NP-tests, i.e. to obtain rapidly results which can be directly taken into account by the healthcare professional, is obvious. However, the problem is that the users, in general, are not qualified in clinical chemistry since they are not laboratory professionals. Some concerns have been expressed that the current requirements of the IVDD are not sufficiently addressing the special circumstances in which PoC/NP-tests are used. According to a study on PoC/NP-tests available on the Dutch market, the technical documentation (risk-analysis and instructions for use) were of good quality in one third of the cases, while in another one third the quality was moderate, and in one quarter of the cases insufficient or absent (the results of the remaining tests being inconclusive)[8].

1.3.3. Alignment with the MDD where appropriate (e.g. medical software)

Directive 2007/47/EC introduced a number of amendments in the MDD/AIMDD which are also relevant for IVDs, in particular as regards the essential requirements for medical software, the incorporation of the relevant essential requirements of the Machinery Directive and the principles of design for patient safety and design for lay, professional, disabled or other users. The revision of the IVDD would therefore give the opportunity to align it with the MDD, where appropriate.

2. OBJECTIVES

The overall objectives pursued by the revision of the regulatory framework for medical devices as set out in the main part of this impact assessment (section 3.1.) are also the guiding principles for the specific issues of the IVDD. These general objectives can be further detailed by the specific objectives set out below. Each of them contributes to the achievement of the overall objectives.

- **Objective IVD-1: Covering of legal gaps and loopholes**

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6 Annex I, A, 3 of the IVDD

7 GHTF/SG1/N045:2008 regarding Principles of In Vitro Diagnostic (IVD) Medical Devices Classification 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".

8 See National Institute for Public Health and the Environment (Netherlands), Point-of-care diagnostic devices: an assessment of safety related technical documentation items, 2010 (RIVM report 360050025/2010).

- **Objective IVD-2: Appropriate and robust classification and conformity assessment of IVDs**

- **Objective IVD-3: Clear and updated legal requirements for enhanced safety and performances of IVDs**

3. POLICY OPTIONS

3.1. Policy options regarding objective IVD-1: Covering legal gaps and loopholes

3.1.1. "In-house" tests

3.1.1.1. Policy option IVD-1A: Delete the exemption for "in-house" tests

Deleting Article 1(5) IVDD would mean that "in-house" tests would be subject to the IVDD and would have to meet the requirements set out in that directive.

3.1.1.2. Policy option IVD-1B: Clarify the scope of the exemption for "in-house" tests and require a mandatory accreditation for "in-house" tests manufacturers

This policy option would amend the current Article 1(5) of the IVDD by defining "health institution" and by deleting the notion of "immediate vicinity". It would allow laboratories that are not located in the immediate geographical area, but belong to the same legal entity, to manufacture "in-house" tests and would require that "in-house" tests manufacturing laboratories are accredited according to ISO 15189[9] or similar requirements. The "in house" tests themselves would remain exempted from the requirements of the IVDD.

3.1.1.3. Policy option IVD-1C: Clarify the scope of the exemption for "in-house" tests, require a mandatory accreditation for "in-house" tests manufacturers and subject high risk (class D) "in-house" tests to the requirements of the IVDD

This option builds upon option IVD-1B but would exclude class D "in-house" tests from the exemption. They would thus be subject to the requirements of the IVDD, in particular the essential requirements (including clinical evidence), conformity assessment procedure and the vigilance system.

3.1.2. Genetic tests

3.1.2.1. Policy option IVD-1D: No legislative change and clarification by guidance

This policy option would not lead to a change of the legal definition of an IVD. The Commission would rather clarify the definition by an interpretation regarding genetic tests through a guidance document.

3.1.2.2. Policy option IVD-1E: Amendment of the legal definition of an IVD to include all tests providing information "obtained by analysis of the genetic material", with a negative list of genetic tests excluded from the IVDD

This policy option would require an amendment of the legal definition of an IVD in order to include in its scope all tests that provide information "obtained by analysis of genetic material". Tests without any medical purpose, such as paternity tests or forensic tests, would need to be explicitly excluded by means of a negative list.

[9] ISO 15189: Medical laboratories – Particular requirements for quality and competence

3.1.2.3. Policy option IVD-1F: Amendment of the legal definition of an IVD to include tests providing information "about the predisposition to a medical condition or a disease"

This policy option would also require an amendment of the legal definition of an IVD in order to include in its scope all tests that provide information "about the predisposition to a medical condition or a disease". This would cover a wide range of predictive genetic tests, but not genetic tests without any medical purpose. A negative list would therefore not be necessary.

3.1.3. Companion diagnostics in personalized medicines

3.1.3.1. Policy option IVD-1G: No legislative change regarding companion diagnostics

With this policy option, companion diagnostics would continue to be regulated as IVDs under the IVDD. If the GHTF classification rules were adopted (see policy option IVD-2B), companion diagnostics would be classified within class C[10]. A Notified Body would be therefore systematically involved in the conformity assessment procedure.

3.1.3.2. Policy option IVD-1H: Regulation of companion diagnostics within the framework of the legislation on medicinal products

This policy option would submit companion diagnostics to the medicinal products legislation and would require the corresponding amendment of Directive 2001/83/EC or the adoption of a specific legislation on companion diagnostics.

3.2. Policy options regarding objective IVD-2: Appropriate and robust classification and conformity assessment of IVDs

3.2.1. Classification

3.2.1.1. Policy option IVD-2A: No change to the classification of IVDs

This policy option would maintain the current system of listing high risk IVDs in Annex II to the IVDD.

3.2.1.2. Policy option IVD-2B: Adoption of the GHTF classification rules and adaptation of the conformity assessment procedures to the relevant GHTF guidance

This policy would require the adoption of the GHTF classification for IVDs[11] which would replace the current list in Annex II to the IVDD. The conformity assessment procedures would need to be adapted accordingly to the relevant GHTF guidance[12].

3.2.2. Batch release verification

3.2.2.1. Policy option IVD-2C: Batch release verification for high risk IVDs by the manufacturer under the control of a Notified Body (legislative clarification)

This policy option would lead to small amendments of the relevant provisions of the IVDD regarding batch release verification, clarifying that the batch release testing is to be performed by the manufacturer under the control of a Notified Body without mandatory testing by an independent laboratory.

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10 Rule 3 of GHTF/SG1/045:2008: IVD medical devices are classified in Class C if they are intended for use: […] in screening for selection of patients for selective therapy and management, or for disease staging, or in the diagnosis of cancer. Example: personalized medicine.

11 GHTF/SG1/N045:2008 regarding Principles of In Vitro Diagnostic (IVD) Medical Devices Classification.

12 GHTF/SG1/N046:2008 regarding Principles of Conformity Assessment of In Vitro Diagnostic (IVD) Medical Devices.

3.2.2.2. Policy option IVD-2D: Systematic batch release verification for high risk IVD by an independent laboratory

This policy option would require an amendment of the relevant provisions of the IVDD to mention that an independent and recognised laboratory would have to perform the verification of manufactured high risk IVDs by batches before they could be placed on the market. It would also imply setting the criteria for the laboratories to be designated to perform such batch release testing.

3.3. Policy options regarding objective IVD-3: Clear and updated legal requirements for enhanced safety and performances of IVDs

3.3.1. Clinical evidence

3.3.1.1. Policy option IVD-3A: No legislative change regarding clinical evidence

This policy option would not lead to amendments of the relevant IVDD provisions with regard to the demonstration of the clinical evidence for the performance evaluation of IVDs.

3.3.1.2. Policy option IVD-3B: Legislative clarification of the requirements for the clinical evidence for IVDs

This policy option would clarify the existing requirements on clinical evidence within a specific annex[13] detailing the analytical and clinical performances to be demonstrated by the manufacturer before placing an IVD on the market. It would be spelled out that the demonstration of the clinical evidence would need to be proportionate to the risk of the IVD. Where appropriate, the clinical evidence would include the demonstration of the negative and positive predictive values[14], based on the prevalence of the disease.

3.3.1.3. Policy option IVD-3C: Legislative clarification of the requirements for the clinical evidence for IVDs and demonstration of the clinical utility

In addition to the demonstration of the clinical evidence, this option would also require the demonstration of the clinical utility of an IVD before its placing on the market. Clinical utility is described as the usefulness of the results obtained from testing with the IVD and the value of the information to the individual being tested and/or the broader population[15]. It would thus require the manufacturer to demonstrate, beyond the scientific validity and the clinical performances of an IVD, how it supports clinical decisions for patient management, such as effective treatment or preventive strategies.

3.3.2. Point-of-care or near-patient IVDs

3.3.2.1. Policy option IVD-3D: No change regarding point-of-care or near-patient IVDs

Policy option 3D would not lead to any clarification of the requirements applicable to point-of-care or near-patient IVDs.

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13 Similar to Annex X of the MDD specifying the requirements regarding clinical evaluation.

14 Negative predictive value is defined as the proportion of subjects with a negative test result who are correctly diagnosed. Positive predictive value (or precision rate) is defined as the proportion of subjects with positive test results who are correctly diagnosed

15 GHTF/SG5(WD)NxR3: Clinical evidence for IVD medical devices – Key definitions and Concepts (state of play: 20 Max 2011).

3.3.2.2. Policy option IVD-3E: Clarification of the legal requirements in respect to point-of-care or near-patient IVDs

On the contrary, policy option 3E would lead to the clarification of the general requirements in order to address specific concerns in relation to point-of-care or near-patient IVDs, in particular regarding the information to be supplied by the manufacturer in the instructions for use. It would also concern the demonstration of the clinical evidence for which the specific conditions of use need to be taken into account (i.e. point of care environment and comparison to comparable tests performed in laboratories).

3.3.3. Alignment with the MDD where appropriate (e.g. medical software)

3.3.3.1. Policy option IVD-3F: no alignment with the MDD

Policy option 3F would not incorporate the relevant modifications introduced in the MDD by Directive 2007/47/EC also into the IVDD.

3.3.3.2. Policy option IVD-3G: Alignment to the MDD where appropriate

On the contrary, policy option 3G would incorporate, where appropriate, the relevant modifications introduced by Directive 2007/47/EC into the MDD also into the IVDD. This would concern the essential requirements for medical software, the incorporation of the relevant essential requirements of the Machinery Directive and the principles of design for patient safety and design for lay, professional, disabled or others users.

4. IMPACT OF POLICY OPTIONS

4.1. Impact of policy options IVD-1A to IVD-1C ("in-house" tests)

Policy option IVD-1A (delete the exemption for "in-house" tests) would ensure a level playing field between "in-house" tests manufacturing laboratories and manufacturers by avoiding unfair competition between them.

However, this option would have a high negative impact on public health since a broad range of "in-house" tests are not commercially available. The removal of the exemption would limit the access to certain tests for European patients and citizens.

During the 2010 public consultation, respondents pointed out that the exemption for "in-house" tests is mainly used by public laboratories to make tests for rare medical conditions, tests for cytogenetic and other whole-genome testing, seldom-use tests for common analytes, alternatives in test methodology or to customize tests for common genetic disorders. The stakeholders underlined that the exemption may also be used for rapid responses to public health treats, e.g. SARS, Influenza H5N1, H1N1. Moreover, the exemption seems also to have a positive impact on the research and development process for IVDs.

No data exists as regards the volume of "in-house" tests or on the number of laboratories using the "in-house" tests exemption ("in-house" tests are usually made in hospitals, but not all hospitals necessarily make "in-house" tests). The extent of "in-house" tests, however, does not seem to be too significant. Postnatal testing for newborn appears to be the most important area of "in-house" tests. According to data provided by the National Health System (NHS) in the United Kingdom, postnatal "in house" tests were used for the testing of 400 disorders. For more than 300 disorders, the number of testing provided was lower than 100 per year. Only testing for 16 disorders were performed more than 1000 times a year. This tends to

demonstrate that a commercial marketing of "in-house" tests to perform such postnatal testing is unlikely to take place, due to the relatively low volume of sales expected.

In addition, respondents highlighted that this policy option would have a significant economic impact on hospitals and on healthcare systems. For example, in the United Kingdom, it is estimated that the mandatory use of CE marked tests for newborn screening laboratories would lead to an additional cost of £6.2 mio./year.

For the above reasons, option IVD-1A is not retained.

Policy options IVD-1B (clarify the scope of the exemption for "in-house" tests and require a mandatory accreditation for "in-house" tests manufacturers) and IVD-1C (same as option IVD-1B and subject high risk (class D) "in-house" tests to the requirements of the IVDD) would clarify which laboratories shall benefit from the "in-house" tests exemption and therefore would reduce the divergences between the Member States. These policy options would also lead to the reduction of borderline cases and of situations of unfair competition for manufacturers.

The deletion of the requirements for "immediate vicinity" would have a positive social impact since "in-house" tests would be allowed to be used on samples taken in other locations and it would address the issue of health institutions with several geographical locations. The suggestion made by some stakeholders to limit the exemption to health institutions belonging to the public sector would not be appropriate since, in some Member States, health institutions may be organised as private bodies. A definition of the term "health institution" to the extent that it shall be understood as a body whose primary purpose is the care or treatment of patients and/or the promotion of public health would be beneficial since it would exclude free-standing laboratories which provide diagnostic services for which the exemption has never been intended.

Both policy options 1B and 1C would align the situations in the Member States by requiring the mandatory accreditation of laboratories according to ISO 15189, or similar requirements. Mandatory accreditation would have an economic impact which consists of the accreditation fees (if any) and the compliance costs to the accreditation standard. The costs could vary between EUR 5,000 and EUR 13,000 for the initial accreditation, if provided by a for profit accreditation laboratory, but it may also be provided by authorities. It is not possible to have a global estimation of the costs as the number of laboratories manufacturing "in-house" tests is not precisely known. It needs to be also noted that many of those laboratories are already accredited, either on voluntary basis or due to national requirements. Mandatory accreditation would have a significant positive impact in terms of safety and quality of the testing process since ISO 15189 requires, among others, that "if in-house procedures are used, they shall be appropriately validated for their intended use and fully documented". Accreditation of laboratories manufacturing "in-house" tests was considered by many stakeholders as a key requirement during the 2010 public consultation.

Policy option IVD-1C would go one step further than policy option IVD-1B by submitting high risk (class D) "in-house" tests to the requirements of the IVDD. The economic impact on laboratories would therefore be higher due to the implementation of these requirements, including the involvement of a Notified Body. This economic impact, however, would need to be balanced with a higher level of health protection. Moreover, such "in-house" tests could be CE marked and therefore marketed within the EU.

Submitting class D devices to the requirements of the IVDD is proportionate from a public health standpoint since any failure of these tests can lead to major public health damages due to the fact that class D devices are mainly intended:

- to be used to detect the presence of, or exposure to, a transmissible agent in blood, cells, tissues or organs in order to assess their safety and their suitability for transfusion or transplantation;

- to be used to detect the presence of, or exposure to, a transmissible agent that causes a life-threatening, often incurable, disease with a high or currently undefined risk of propagation;

- to be used for blood grouping or tissue typing to ensure the immunological compatibility in case of transfusion or transplantation.

Those devices correspond largely to the tests currently listed in Annex II list A of Directive 98/79/EC, for which the intervention of a Notified Body is already required before their placing on the European Union market. Most of them are usually commercially available on the European Union market. In addition, in case of emergency situations where class D tests would need to be quickly deployed, the specific provision[16] of Directive 98/79/EC (that allows competent authorities to authorise the placing on the market within their territory of devices for which the conformity assessment procedures have not been carried if the use of such tests is in the interest of protection of health) would be maintained and clarified in order to avoid any risk of shortage. Last but not least, this option would also ensure harmonised safety and performance requirements for class D IVDs throughout Europe in a context of increasing mobility of patients, in particular due to the implementation of Directive 2011/24/EU on patients' rights in cross-border healthcare.

Option IVD-1B could be considered as the minimum requirement to be set. Option IVD-1C, however, is considered the preferred option because it ensures a higher level of safety and a harmonised level of safety and performances for high risk IVDs, regardless of the place of manufacture in the Internal Market.

4.2. Impact of policy options IVD-1D to IVD-1F (genetic tests)

The option IVD-1D (no legislative change) would not change the *status quo*. Even if the Commission intended to clarify which genetic tests were covered by the IVDD, such guidance would not be legally binding and would not enhance the legal certainty. This option would therefore not be effective and should be discarded.

Policy option IVD-1E (amendment of the legal definition of an IVD to include all tests providing information "obtained by analysis of the genetic material", with a negative list of genetic tests excluded from the IVDD) would considerably extend the scope of the IVDD and would therefore require exclusions by means of a negative list. Such a list would require to be regularly updated to the technological development. Due to the length of legislative procedures, this approach would bear the risk that certain non-medical tests – if not included in the negative list – would become subject to the IVDD even though the essential requirements, including the requirements regarding clinical evidence and risk/benefit analysis,

[16] Article 9(12) of Directive 98/79/EC.

would not be appropriate. This option would therefore not be an adequate means to address the problem and should also be discarded.

Policy option IVD-1F (amendment of the legal definition of an IVD to include tests providing information "about the predisposition to a medical condition or a disease") would constitute a moderate extension of the IVDD. It would lead to a legal certainty favourable to the Internal Market without including genetic tests that do not have any intended medical purpose. The economic impact would be that manufacturers of genetic tests which currently escape from the IVDD due to legal uncertainty would clearly be covered and would need to demonstrate compliance, usually with the involvement of a Notified Body in the conformity assessment procedure. Genetic tests which would not satisfy the safety and performances requirements of the IVDD would disappear from the market. This would be a desired consequence of this option since it would lead to a high level of protection of public health against low quality genetic tests which do not provide reliable results. Due to the positive social impact, which outweighs possible economic costs for some manufacturers, policy option IVD-1F is the preferred option and should be retained[17].

4.3. Impact of policy options IVD-1G to IVD-1H (companion diagnostics)

During the 2010 public consultation, the respondents almost unanimously expressed the view that companion diagnostics should continue to be regulated under the IVDD which would back policy option IVD-1G (no legislative change).

Option IVD-1H (regulation of companion diagnostics within the framework of the legislation on medicinal products) would lead to en extension of the competences of the European Medicines Agency or of the national medicinal products agencies since the clinical validity of the companion IVD would be part of the assessment of the medicinal product in the context of the marketing authorisation. This option may lead to problems for IVDs that have several intended uses and might submit them to two different regulatory regimes. This option was not supported by stakeholders during the 2010 public consultation. In addition, a regulation under the medicinal products legislation would imply developing the companion diagnostic at the same time as the medicinal product, which would significantly increase the time to market and subject the manufacturers of companion diagnostics to high regulatory burdens and make them (more) dependent on the manufacturer of the medicinal product. It could therefore negatively impact the competition and the development of innovative tests. Option IVD-1H should be therefore discarded.

Policy option IVD-1G, to the contrary, would not add any burden on economic operators. In case of the adoption of the GHTF classification rules (see policy option IVD-2B), the regulation of companion diagnostics under the IVDD would ensure an appropriate level of safety and performances for these products. Therefore policy option IVD-1G is the preferred option and should be retained.

4.4. Impact of policy options IVD-2A to IVD-2B (classification)

Policy option IVD-2A (no legislative change) would maintain the *status quo*, i.e. a list of high risk IVDs in an annex to the IVDD. It would keep the high level of legal certainty as regards the IVDs subject to the strictest conformity assessment procedure. However, it would not automatically classify newly developed IVDs in the appropriate risk class, but would require

[17] This option is also in line with recent enhanced control by the US FDA of genetic tests offered direct to consumers, see Clinica, June 2011, p. 6: "US FDA scrutiny of DTC genetic tests continues".

legislative action (possibly through amendment of the annex to the IVDD by delegated act). Option IVD-2A should be therefore discarded.

Policy option IVD-2B (adoption of the GHTF classification rules and adaptation of the conformity assessment procedures to the relevant GHTF guidance), on the contrary, would move the classification to a rules-based risk classification system as it exists already for the other medical devices, classifying IVDs into 4 risk class as follows:

1. GHTF classification system for IVDs

2.

CLASS	RISK LEVEL	EXAMPLES
A	Low Individual Risk and Low Public Health Risk	3. Specimen receptacles
B	Moderate Individual Risk and/or Low Public Health Risk	Pregnancy self testing
C	High Individual Risk and/or Moderate Public Health Risk	Blood glucose self testing
D	High Individual Risk and High Public Health Risk	HIV test

The classification rules have been developed at GHTF level (GHTF/SG1/N045:2008) and have been implemented so far by Australia. They are accompanied by GHTF principles on conformity assessment (GHTF/SG1/N046:2008). The adoption of the GHTF classification system would enhance the robustness of the regulatory framework to technological progress since innovative IVDs would automatically be classified in the appropriate risk class. This would lead to a considerable increase in the protection of public health and patient safety. A timely access to market of innovative IVDs would be ensured. In addition, it would constitute an important step towards international harmonisation in the field of IVDs, and thus facilitate trade in this sector.

The adoption of the GHTF classification and of the conformity assessment schemes for IVDs, altogether would lead to an increased involvement of Notified Bodies in the conformity assessment process. It will ensure the safety and performances of IVDs placed on the EU market. However, it will lead to costs for manufacturers of most class B IVDs and class C IVDs which, under the current legislation, are able to certify the conformity of their products themselves (self-certification). No or only little impact can be expected for IVDs of class A (they would remain under self-certification) and of class D (they correspond largely to the IVDs currently listed in Annex II, list A, of the IVDD).

Industry considers that class B IVDs and class C IVDs represent respectively around 50% and 35%, of the 40,000 IVDs present on the European market, *i.e.* 20,000 class B IVDs and 14,000 class C IVDs.

The following costs estimation related to the adoption of the GHTF classification system is based on data from 11 manufacturers provided by the European Diagnostics Manufacturer Association (EDMA).

Under the GHTF system, the Notified Bodies would need to assess the manufacturer's quality system in case of class B IVDs. The estimated initial costs related to a classification in class B, which include Notified Body fees, updating of technical documentation and changes to the

labelling, would range from EUR 1,100 to EUR 2,059 (weighted medium: EUR 1,220). It means that the adoption of the GHTF classification system and the corresponding changes to the conformity assessment procedures would have an initial economic impact of around EUR 24mio. for class B IVDs manufacturers.

For class C IVDs, in addition to the quality system assessment, the Notified Bodies would need to examine also the design documentation. This could either be done for every IVD or, by analogy to the requirements for class IIb devices under the MDD, on a representative basis for each generic device group. In the costs estimation, only 9,800 out of the 14,000 class C IVDs have been taken into account since around 30% of IVDs which would fall into class C according to GHTF rules are already today subject to conformity assessment with the involvement of a Notified Body (because they either belong to Annex II, list B, of the IVDD or are IVDs for self-testing). The initial economic impact related to a classification in class C, which again include Notified Body fees, updating of technical documentation and changes to the labelling, would range from EUR 12,000 to EUR 26,190 (weighted medium: EUR 14,906).

30% of the above mentioned costs would be recurrent due to annual surveillance audits. 60% of the costs would recur every 5 years for the renewal of certificates.

The following table provides an overview the yearly costs, over 5 years, in case of adoption of GHTF classification model and conformity assessment for the IVD sector

Yearly costs for adoption of GHTF classification and conformity assessment for the IVD sector

	Year 1 (submission of documentation to a Notified Body for pre-market assessment and labelling adjustments)	**Year 2 (annual surveillance)**	**Year 3 (annual surveillance)**	**Year 4 (annual surveillance)**	**Year 5 (renewal of certificates)**
Class B ca. 20000	EUR 24 mio.	EUR 7.2 mio.	EUR 7.2 mio.	EUR 7.2 mio.	EUR 14.4 mio.
Class C ca. 9800	EUR 146 mio.	EUR 43.8 mio.	EUR 43.8 mio.	EUR 43.8 mio.	EUR 87.6 mio.

The total initial economic impact of the change of the classification system could therefore be estimated at around EUR 170 mio. To a large extent, these costs are related to the submission of documentation to a Notified Body for pre-market assessment or labelling adjustments and are therefore also mentioned in the chapter on administrative costs in the main part of this impact assessment.

To mitigate the economic impact on manufacturers, a sufficient transitional period (*i.e*. 5 years) should be foreseen. In addition, the classification according to internationally recognised rules would lead to benefits in terms of competitiveness due to international harmonization, provided that the GHTF classification rules were adopted as such. It is impossible to provide hard figures as regard the economic benefits for manufacturers deriving from the adoption of the GHTF classification rules. But the IVD industry itself expects

simplification of regulatory procedures in third countries (especially smaller markets) as well as in the EU.

The disadvantage of a rules based classification system, *i.e.* the need to determine the class on a case-by-case basis, would need to be addressed by a quick and EU-wide uniform mechanism to settle classification questions (see policy option 3B in the main part of the impact assessment).

The current conformity assessment modules of the IVDD, to a large extent, are in line with the GHTF principles on conformity assessment. However, some concerns were raised during the 2010 public consultation regarding the procedure laid down in Annex VI of the IVDD since it does not include an assessment of the vigilance system of the manufacturer. It would therefore need to be amended accordingly. Moreover, according to the feedback from respondents to the 2010 public consultation (which confirmed findings from a 2008 survey among Notified Bodies), the conformity assessment procedure laid down in Annex VI (EC verification in case of type-examination) is not used by manufacturers. Moreover, Annex VI does not require manufacturers of high risk IVDs to put in place a quality system which is contradictory to the fact that, even in the case of self-certification, manufacturers must have a quality system. It is therefore suggested deleting this module in order to increase patient safety while simplifying the conformity assessment pathways, without significant impact on economic operators.

In view of the above, the replacement of the current Annex II listing system by the GHTF classification rules, coupled with some adaptations of the conformity assessment procedures, would be considered beneficial in terms of robustness of the regulatory system and would ensure a high level of protection of public health. Option IVD-2B is therefore the preferred option and should be retained. Despite the economic impact on manufacturers, this option was also supported by 87% of the respondents to the 2010 public consultation (88% of the competent authorities, 88% of the manufacturers, 87% of the clinical laboratories and medical associations, 83% of hospitals, 100% of genetic associations and notified bodies). The manufacturers' support was expressed both by SMEs (*e.g.* Bactus AB[18]) and by larger companies (*e.g.* Roche, Johnson & Johnson).

The costs would be compensated by the positive impact in terms of public health and safety and by advantages in terms of competitiveness deriving from a move towards harmonization with Europe's main trade partners, which is of utmost importance since the majority of IVD manufacturers market their products both in and outside the European Union . Adoption of the GHTF classification rules would also meet the Council's request to improve the system of risk-based classification particularly for IVDs[19].

4.5. Impact of policy options IVD-2C to IVD-2D (batch release verification)

The concept of batch release verification for high risk IVDs as such was not questioned during the 2010 public consultation, but clarification was considered necessary regarding how and by whom the testing of batches before release onto the market should be performed, in order to eliminate the current discrepancies in the implementation of this concept. The majority of stakeholders underlined that batch release testing should be performed by the manufacturer in the context of the quality management system under the supervision of a

[18] Swedish company manufacturing IVDs falling under classes B and C according to GHTF classification system

[19] Council Conclusions adopted on 6 June 2011, section 6, 2nd indent.

Notified Body and that additional testing of batches performed by an independent laboratory would only be a duplication of the testing already performed by the manufacturer.

Batch release testing by an independent laboratory has a significant cost. According to data provided by the European IVD industry, policy option IVD-2D (systematic batch release verification for high risk IVD by an independent laboratory) would likely have the following impact:

it is estimated that class D (i.e. Annex II, list A) IVDs represent roughly 5 to 10% of the number of IVDs on the market. According to data provided by economic operators, the cost of testing a batch performed by an independent laboratory may vary between EUR 1,000 and EUR 1,500 for each batch, compared to a fee range from EUR 100 to EUR 200 when the testing is performed by the manufacturer under the supervision of a Notified Body.

The number of batches manufactured for class D IVDs ranges from around 10 to 50, depending on the shelf-life of the IVDs. The tests used for the determination of blood grouping have a short shelf-life and it is estimated that a new batch of these products is manufactured each week. It was not possible to have an idea of the repartition between class D IVDs with a high number of batches produced each year and those requiring a lower number of batches.

Number of class D IVDs on the market	**Estimated number of batches per year**	**Cost for a batch release testing performed by an independent laboratory**	**Cost of a batch release testing performed by manufacturer under the supervision of a Notified Body**
2,000 to 4,000	10 to 50	1,000€ to 1,500€	100€ to 200€
Total costs/year		**20-300mio.€**	**2-40mio.€**

The above table shows that the cost for batch release testing by an independent laboratory may be up to 10 times higher than testing by the manufacturer under the control of a Notified Body. Option IVD-2D would therefore lead to additional costs of between EUR 18mio. and EUR 260mio., with an important impact on manufacturers of IVDs used for the determination of blood grouping.

These costs could have been justified in case of added value for the protection of public health. However, despite long-lasting discussions on this issue and an explicit question in the 2010 public consultation, no strong evidence has been provided so far that the batch release verification by an independent laboratory would actually identify a meaningful number of low-quality and/or unsafe batches of high risk IVDs. Option IVD-2D should be therefore discarded.

Option IVD-2C (batch release verification for high risk IVDs by the manufacturer under the control of a Notified Body (legislative clarification)) would ensure an appropriate level of protection of public health while leading to some savings for manufacturers since it would be clarified that batch release testing by an independent laboratory could not be required by the individual Member States.

In view of the above, option IVD-2C is considered the preferred option and should be retained. The clarification that batch release verification is to be done by the manufacturer under the control of a Notified Body should be accompanied by additional requirements regarding the methods, the reference materials and the panels used for the batch release testing which should be approved by the Notified Body. A network of reference laboratories might be set up to provide scientific expertise for the development of testing methods to be specified in Common Technical Specifications for high-risk IVDs and to define other aspects related to the state of the art. They could also organise sample testing in the context of market surveillance activities.

4.6. Impact of policy options IVD-3A to IVD-3C (clinical evidence)

Policy option IVD-3A (no legislative change regarding clinical evidence) would not lead to an improvement of the current regulatory situation, which is perceived by almost 90% of the respondents to the 2010 public consultation as not sufficiently clear since it is understood by many as setting only requirements regarding the analytical validity of the IVDs. The respondents of the 2010 public consultation rather suggested that the requirements regarding the clinical evidence needed for IVDs should be more detailed in the legislation (by adding a specific Annex on clinical evidence to the IVDD[20]) and adapted to the different risk classes. The future EU requirements should be aligned with GHTF guidance on clinical evidence which is currently under preparation. Option IVD-3A would not achieve this objective and should therefore be discarded.

Option IVD-3B (legislative clarification of the requirements for the clinical evidence for IVDs) would lead to a clarification of the legal requirements on the demonstration of clinical evidence and would therefore eliminate divergences regarding the interpretation of the current provisions which contribute to a fragmentation of the Internal Market. This would also provide more reliable and precise information to the users and would therefore have a positive impact in terms of protection of public health. The economic impact of such requirements is considered negligible because these data should already be part of the technical documentation of IVDs placed on the EU market. However, there may be cases where the demonstration of the clinical evidence would not be proportionate, for example for some genuinely innovative tests for which clinical performances may only be established after a certain period of "real use" experience. The legislation should therefore make provision that, for "new"[21] tests, the requirement to demonstrate clinical performances could be delayed to a moment after its placing on the market, if duly justified either by the specific characteristics of the IVD or on the ground of public health protection. Option IVD-3B would therefore be an effective and proportionate mean to clarify the concept of clinical evidence in the IVDD.

Policy option IVD-3C (same as policy option IVD-3B and introduction of the concept of "clinical utility") would go further and would make the demonstration of the clinical utility of an IVD a precondition for its placing on the market. A broad majority of respondents expressed their opposition to this option during the 2010 public consultation. They underlined that the demonstration of the clinical utility was a moving concept, evolving with the scientific progress, and should rather be determined by the user (i.e. the healthcare professional) on a case-by-case basis, depending on the context in which the test is used.

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[20] In the MDD and AIMDD, a specific annex exists for clinical evaluation.

[21] The concept of "new product" is already used in Article 10(4) of the IVDD but would need to be clarified.

Certain IVDs are intended to provide general information on a physiological state of a person, such as the level of calcium in blood. The clinical utility, however, would depend on other factors outside the manufacturer's remits and the intended use. Moreover, it might be nearly impossible to demonstrate the clinical utility of most innovative tests. Respondents to the 2010 public consultation therefore were of the opinion that such a requirement would negatively impact the development and the placing on the market of innovative IVDs. However, it needs to be acknowledged that manufacturers often need to demonstrate the clinical utility for reimbursement purposes. It is therefore argued that it could make sense to require the demonstration of the clinical utility already at the time of the placing on the market. This position, however, does not take into account that reimbursement policy falls within the competences of the Member States and should be clearly distinguished from the regulatory purposes of the IVDD. It would also lead to delayed access to market which would likely be detrimental for manufacturers but also for patients and users. Policy option IVD-3C would therefore not be proportionate and should be discarded.

In light of the above, option IVD-3B is the preferred option and should be retained.

4.7. Impact of policy options IVD-3D and IVD-3E (PoC/NP-tests)

Policy option IVD-3D (No change regarding point-of-care or near-patient IVDs) would not solve the problems that have been identified and should therefore be discarded.

On the contrary, policy option IVD-3E (clarification of the legal requirements in respect to point-of-care or near-patient IVDs) would spell out in the essential requirements, in particular in the context of the information to be supplied by the manufacturer, that the specific circumstances of use of these tests need to be taken into account by the manufacturers in the context of the risk-analysis and in the instructions for use. The option would not introduce new requirements on manufacturers but would rather specify the aspects specifically applicable to PoC/NP-tests. It would clarify the rules and facilitate the functioning of the Internal Market. It would lift the safety and performances level to the level of those manufacturers who already comply with the legal requirements and the spirit of the legislation. As it was shown in the study of the Dutch National Institute for Public Health and the Environment (RIVM)[22], around 33% are already in compliance while the rest is not. The economic impact would not be significant but policy option IVD-3E would have a positive impact on public health protection as well as on the Internal Market and should therefore be retained.

4.8. Impact of policy options IVD-3F and IVD-3G (alignment with the MDD)

Policy option IVD-3F (no alignment with the MDD) would maintain the *status quo* and would leave legal discrepancies, potentially leading to legal uncertainties, between the MDD and the IVDD. Policy option IVD-3F should be therefore discarded.

On the contrary, policy option IVD-3G (alignment with the MDD where appropriate) would not add new requirements on manufacturers but would take over, where appropriate, improvements introduced into the MDD by Directive 2007/47/EC also into the field of IVDs. The requirements are already inherent in the essential requirements but by spelling out specific requirements on medical software or regarding the design principles, manufacturers will have a clearer legal basis on which they need to base their risk-benefit analysis. Again,

[22] See footnote 8

the economic impact would not be significant but policy option IVD-3G would have a positive impact on public health protection and should therefore be retained.

5. CONCLUSIONS

The following policy options are the preferred ones for specific aspects related to the revision of the IVDD:

- Option IVD-1C: Clarify the scope of the exemption for "in-house" tests, require a mandatory accreditation for "in-house" tests manufacturers and subject high risk (class D) "in-house" tests to the requirements of the IVDD
- Option IVD-1F: Amendment of the legal definition of an IVD to include tests providing information "about the predisposition to a medical condition or a disease"
- Option IVD-1G: No legislative change regarding companion diagnostics
- Option IVD-2B: Adoption of the GHTF classification rules and adaptation of the conformity assessment procedures to the relevant GHTF guidance
- Option IVD-2C: Batch release verification for high risk IVDs by the manufacturer under the control of a Notified Body (legislative clarification)
- Option IVD-3B: Legislative clarification of the requirements for the clinical evidence for IVDs
- Option IVD-3E: Clarification of the legal requirements in respect to point-of-care or near-patient IVDs
- Option IVD-3G: Alignment with the MDD where appropriate

Most of the policy options suggested for the revision of the IVDD are clarifications of existing provisions. Their economic impacts are estimated to be insignificant, while the positive impact on public health and on the functioning of the Internal Market is high.

Policy option IVD-2B (adoption of GHTF classification rules), however, would significantly increase, in absolute terms, the costs for manufacturers to bring an IVD to the market. Nevertheless, broken down on each manufacturer, the costs do not appear unreasonably high. The higher costs would be due to the increased involvement of Notified Bodies in the conformity assessment procedure which would considerably lift the level of assurance of the safety and performances of IVDs for the benefit of public health and perception of the IVD sector as a whole. Enhanced robustness of the classification system, as well as international harmonisation, are additional advantages achieved by this option which, altogether, would compensate for the higher costs.

Combined with the improvements of the horizontal aspects pursued by the revision of the entire regulatory framework for medical devices (Notified Bodies' oversight, enhanced transparency, strengthened post-market safety, statutory Medical Device Expert Group etc.), the suggested policy options for the revision of the IVDD would lead to a modern set of rules for IVDs which would ensure a high level of public health, facilitate the functioning of the

Internal Market (e.g. clearer rules, predictability, uniform interpretation) and support the innovativeness and competitiveness of the IVDs manufacturers.

6. MONITORING AND EVALUATION

As mentioned under section 5, the policy options suggested for the revision of the IVDD are mostly legal clarifications of existing provisions (e.g. clarifications on clinical evidence of IVDs, on batch testing, on "in-house" tests).

For most of them, the indicator of success will be therefore the reduction of divergences within the European Union regarding the interpretation of the corresponding provisions of the IVDD and an increased legal certainty for stakeholders.

However, to monitor and evaluate the implementation of the future legislative act concerning IVDs in respect to the specific issues discussed in this Annex 2, the following indicators can be taken into account:

6.1. Scope of the IVDD

6.1.1. "In-house" tests

Currently, laboratories that manufacture "in-house" tests may or may not be accredited. An indicator of success for policy option 1C would be an increased number of laboratories manufacturing "in-house" tests accredited according to ISO 15189, or similar requirements.

The accreditation requirement, together with the fact that class D "in-house" will be submitted to the requirements of the IVDD, should improve the level of safety and performances of "in-house" tests manufactured in the European Union, and therefore contribute to a higher level of patient safety. An increased level of safety and performances of "in-house" tests manufactured in the European Union will be an indicator of success of policy option 1C.

The introduction of a definition for "health institution" is expected to increase the legal certainty and to avoid diverging, and sometimes too broad, interpretation of this notion in the European Union. An indicator of success of policy option 1C will be that situations that may come about whereby certain tests are unduly considered as "in-house" tests, escape from the IVDD and might have an insufficient level of safety and performances, would no longer occur.

6.1.2. Genetic tests

An indicator of success for policy option 1F would be a decreased number of borderline cases in terms of qualification of genetic tests.

This policy option should also lead to a higher level of health protection since any genetic test pursuing a medical purpose will have to fulfil the requirements of the IVDD. An indicator of success of policy option 1F will be the disappearance from the European Union market of low quality genetic tests which, while pursuing a medical purpose, do not provide reliable results.

6.2. Classification of IVDs

Indicators of success for policy option 2B would be a smooth transition to the new classification system for IVDs, accompanied by a limited number of borderline cases in terms of risk classification.

A higher level of safety and performances of IVDs is also expected due to the greater than before involvement of Notified Bodies in the conformity assessment process. A lower number of vigilance cases related to IVDs will be an indicator of success for policy option 2B.

The change toward a classification system according to internationally recognised rules should lead to benefits in terms of competitiveness due to international harmonization. A facilitated international trade in the IVD sector would be therefore an indicator of success of policy option 2B.