

EU Proposals for Revising Directive 98/79 of the European Parliament and of the Council of 27 October 1998 on *In Vitro* Diagnostic Medical Devices

Response from the PHG Foundation to the tabled amendments to draft EU regulations on *in vitro* diagnostic medical devices (IVDDR)

Introduction

The PHG Foundation is a non profit making genomics and health think-tank based in Cambridge, UK. Our overarching purpose is to foster and enable the application of biomedical science, particularly genome-based technologies, for the benefit of human health. Among our specific objectives is the promotion of a social and regulatory environment that is receptive to innovation, without imposing an undue or inequitable public burden. The PHG Foundation has a particular interest in the way that new technologies, especially those relating to genomics, are translated within health services and in the impact of genomics upon clinical and public health services.

General Comments

1. A number of European Union Committees have submitted draft reports proposing amendments to the draft IVD and Medical Devices Regulations published last September. As well as publishing reports, each of these committees (Environment, Public Health and Food Safety (ENVI); Internal Market and Consumer Protection (IMCO); and Employment and Social Affairs) have tabled supplementary amendments for discussion. Taken together, these amendments have substantive implications which we address below as an aid to stakeholders and to inform decision making and the legislative process over the next few months. This note supplements the PHG Foundation response circulated in November 2012 and our consultation response to the MHRA consultation earlier this year¹.
2. In these comments we focus on the amendments (numbered 1-399) to the *in vitro* diagnostic medical devices regulation rather than those to the medical devices regulation. The selected amendments are illustrative rather than representing an exhaustive analysis of the impact of all 399 amendments. In the following sections, we have prioritised the issues arising from the draft amendments in terms of their potential impact upon publicly funded health care within the UK. For ease of reference we include the text of the proposed amendments in Appendix one.
3. Our main concern is that the draft IVDD Regulation and amendments do not take account of the potential uses of genetic testing outside of inherited diseases: genetic testing is likely to be used as an adjunct to making a diagnosis and identifying appropriate interventions across the whole length of the patient pathway (from prevention, screening, diagnosis, treatment and prognosis) across a

¹ EU Proposals for Revising Directive 98/79 of the European Parliament and of the Council of 27 October 1998 on *In Vitro* Diagnostic Medical Devices: Response from the PHG Foundation to the draft EU regulations on medical devices (MDR) and *in vitro* diagnostic medical devices (IVDDR) 21.11.12; EU Proposals for Revising Directive 98/79 of the European Parliament and of the Council of 27 October 1998 on *In Vitro* Diagnostic Medical Devices. MHRA Consultation Response from the PHG Foundation to the draft EU regulations on medical devices (MDR) and *in vitro* diagnostic medical devices (IVDDR) 21.1.13

wide breadth of clinical medicine. In this context, singling out genetic testing for exceptional protection may be scientifically questionable and ethically unsound.

Genetic tests (ENVI Amendments 18, 30, 120, 144 and IMCO Amendment 5)

4. Amendment 18 introduces a definition of a genetic test (to amend Article 2 (12a)) to mean '*a test that is carried out for health purposes, involving analysis of biological samples of human origin and aimed specifically at identifying the genetic characteristics of a person which are inherited or acquired during early prenatal development*'. Amendment 120 clarifies that a genetic test as defined by the Regulation is an in vitro diagnostic medical device. We prefer this formulation.
5. Amendment 30 establishes specific requirements for performing genetic tests. It requires that the test must be conducted by medically qualified personnel and that before using the device, the test subject shall be provided with appropriate information on the nature, significance and implications of the genetic test and shall be provided with appropriate and comprehensive genetic counselling including ethical, social, psychological and legal aspects.
6. We are concerned that these requirements are contrary to the development of good medical and professional practice within clinical genetics in the UK and have the potential to significantly limit the potential for genomic technologies to promote better health care. In the UK, accredited genetic counsellors are widely used to deliver genetic counselling, supported by guidance from medical practitioners. However, a narrow interpretation of this amendment, that medical practitioners should '*conduct*' the test restricts the delivery of genetic counselling to members of the medical profession and excludes this highly trained group of health care professionals. It could therefore have the effect of fettering professional development in the UK.
7. There is an extensive literature on the ethical basis of delivering genetic testing to patients. In the UK, it is lawful for patients to proceed with testing on the basis that they are not fully informed about the risks and benefits of the test (if this is a personal choice). Sometimes family members disagree about whether testing should proceed and individuals exert their right not to know a genetic diagnosis. Enacting Amendment 30 in its current form would mean that clinical geneticists could not exert their professional judgement in these matters.
8. As currently drafted, Amendment 30 also has serious potential to undermine the practice of clinical genetics in the UK, and to hinder the diffusion of potentially beneficial technologies that use genetic or genomic tests into other clinical areas (and use by cardiologists, paediatricians or within lipid clinics). Within each of these areas within the UK, non-medically qualified professionals deliver genetic tests to at-risk individuals (e.g. for, various cardiac genetic conditions such as cardiac myopathies and familial hypercholesterolaemia).
9. This amendment might also hinder the development of good professional practice many clinical areas, as a response to the development of novel genomic technologies. For example, whole genome sequencing technologies are becoming increasingly affordable, effective and reliable. As these technologies are introduced, whole genome sequencing could become a first line investigation in a variety of clinical areas. There is a world-wide debate currently underway concerning the form that consent should take where a test is used across multiple conditions. This debate has not yet been resolved. This amendment has the potential to fetter future professional development in this area. Amendment 144

allows more discretion for professional practice, but this might still be disproportionate depending on the type of genetic test.

10. In combination, these amendments would also make access to direct to consumer genetic tests (as defined by the Regulation) unlawful, given that many tests that are available on a DTC basis are neither '*conducted by persons admitted to the medical profession*' and those accessing the test are not provided with '*appropriate and comprehensive genetic counselling*'. The regulatory challenges arising through direct-to-consumer genetic tests were extensively reviewed by the Human Genetics Commission in 2007 and subsequently in 2009. As a result of these reviews, a voluntary framework was drawn up establishing regulatory principles based upon the risks and the benefits associated with various classes of test². This has the advantage of being proportionate to the likely risks and harms associated with each type of test, and also recognises the difficulties of enforcement associated with DTC tests that are accessed by individuals from their own computers.

Requirements for Consent (ENVI Amendments 6-7, 30 and 144)

11. We are concerned that the requirements for an explicit consent for all instances of genetic testing are excessive and disproportionate. It is certainly true that there is a subset of genetic tests for inherited conditions, where the risks and burdens associated with testing need to be fully understood. This is particularly the case for inherited conditions that are caused by a single dominant or recessive gene, especially if predictive tests are carried out before symptoms arise. However increasingly genetic tests are being developed within other clinical specialities. Examples include genetic testing of the cancer genome to track tumour progression, or to clarify potential tumour sensitivity to therapeutic agents. Other applications might include using a battery of common genetic variants that are associated with common complex diseases, such as heart disease, diabetes or cancer predisposition to guide therapeutic interventions such as screening.
12. Granting DNA tests this unique status in legislation ignores the fact that other types of assay (such as proteomics) have similar discriminatory potential. These proposed amendments demonstrate a degree of genetic exceptionalism which is out of step with current scientific applications.

Definition of Medical Devices (ENVI Amendment 14, IMCO Amendment 4))

13. **Indirect benefit:** Amendment 14 amends the definition of medical devices to include devices that have an indirect medical purpose, including indirect impacts on health. This potentially widens the scope of these regulations to all devices that have some indirect effect on lifestyle or behaviour through information provision. This could result in an expansion in the scope of the regulation, and foster legal argument about what falls in and out of scope, without achieving the aim of improving patient safety.
14. **Predictive tests:** These amendments propose increasing the regulatory scope of the IVDDR to include predictive genetic tests. We support this amendment.

The requirement for ethical approval for clinical performance studies (ENVI Amendment 4 Amendment 53, ENVI Amendment 100 and ENVI Amendment 280)

² Human Genetics Commission (2010) A Common Framework of Principles for Direct-to-Consumer Genetic Testing.

15. Creating a statutory requirement for ethical review of all interventional clinical performance studies (or all clinical performance studies in the case of ENVI Amendment 100) is disproportionate. Even studies which are not interventional may still carry risks associated with the processing, sharing and posting of data, and so the concept of a 'risk-free' study is naïve. What matters is that the risks to individual participant are proportionate to the overall benefits to both the individual and to society more generally.
16. It is also important that the processes for developing new tests and devices are as streamlined as possible, and that disproportionate hurdles are not put in place. The societal effect of imposing unnecessary bureaucratic 'hoops' has the potential to bring development to a halt, and there are opportunity costs associated with delaying the development of potentially beneficial products.

Derogation for in-house testing (ENVI Amendments 20 83, 141, 142 and IMCO Amendment 11 and 62)

17. In our consultation response to the draft IVDD regulation we noted that lack of clarity regarding the definition of a 'single health institution' could result in this provision being problematic to implement. 'Making available on the market', 'placing on the market' and 'putting into service' are defined at Articles 2(13), 2(14) and 2(15) respectively. We noted the ambiguities relating to the interpretation of commercial activity in relation to these sections when read together, and the determinative factor appears to be whether the health institutions operate a single quality management system (Article 4(5)).
18. Amendments ENVI 20 and IMCO 11 further attempt to clarify the scope of the exemption for in-house testing. The ENVI amendment excludes commercial clinical service laboratories from the definition of health institution: the IMCO amendment offers an alternative definition, such that only clinical or commercial pathology laboratories which do not have health care or the promotion of public health as their primary purpose are excluded. This would seem to allow for the 'in-house exemption' to be utilised where a test is provided by one part of the NHS for another. However legislators should note that some NHS hospitals are contracting out their pathology and genetic services to commercial contractors (e.g. Serco). Adopting the ENVI amendment might cause a *de facto* lack of harmonisation within the NHS. Amendment ENVI 80 limits the scope of this exemption to a single site. Within the UK, health care is often delivered from Foundation Trusts which operate laboratory provision across a series of sites, and adopting this amendment would inappropriately limit the scope of the 'in-house exemption'.
19. The exclusion of Class D devices from the in-house exemption has the potential to severely curtail the development of devices which address the urgent or unmet medical needs of patients such as emerging pathogens and rare diseases. For this reason we strongly support amendments 83,141 and 142 which recognise the importance of this public health function whilst ensuring patient safety. (IMCO amendment 62 similarly recognises the public health imperative of developing devices speedily for transfusion or transplantation purposes).

Companion Diagnostics (ENVI Amendments 117, 260, 262, 345, 391, 392, 394 and 395)

20. Our view is that companion diagnostics are likely to become much more widely used over the next decade, as pharmaceutical companies turn to more comprehensive genotyping of research participants in order to target drugs more effectively and to minimise adverse events. In the short to medium term, the

development costs associated with companion diagnostics suggests that they will be used to target expensive medicinal products, or to treat serious medical conditions. However, we suggest that the current definition of selecting patients for targeting therapy could be too narrow: companion diagnostics could also be used to monitor response to treatment in order to improve safety and effectiveness. If this definition were adopted, we consider that it would be disproportionate to categorise all companion diagnostics as Class D.

21. It is important that the processes for the co-production of companion diagnostics and therapeutic agents are well worked out. We broadly support the amendments which have been tabled by Anna Rosbach which encourage the use of Common Technical Specifications for the development of companion diagnostics in conjunction with advice from reference laboratories.
22. Whilst it is important that the development and use of companion diagnostics is supported by a robust evidence base, we are concerned that the requirement to prove demonstrable clinical utility, coupled with a positive or negative test result on patient care and positive health outcomes, is too high a threshold for development.

Risk classification, prognosis and novelty (ENVI Amendments 112, 387 and 389)

23. There have been a number of proposals seeking to modify the risk classification rules. We support the amendments that increase the scope of the regulation to include genetic tests that will be used for prediction and prognosis (amendments 112 and 387). However, other amendments introduce novelty as the basis for upgrading a risk classification (e.g. ENVI 389 which provides for tests which are classified as Class B by default should be upgraded to Class C if novel). Novel tests do not necessarily pose increased risks, and such an approach is inconsistent and may be disproportionate. No definition of 'novelty' is contained in the regulation.

The requirement for appropriate counselling and self-testing (ENVI Amendment 347)

24. Amendment 347 provides for self testing to proceed only after appropriate counselling by medical practitioners. The justification for this amendment is that the results of testing can be harmful. If this requirement were narrowly interpreted, the words 'by medical practitioners' would not include counselling by health professionals who are under medical guidance such as genetic counsellors. The requirement for appropriate counselling by medical practitioners is undoubtedly justified in respect of the small number of inherited diseases where a positive test result confers a substantial risk of ill health or disease. Similarly direct medical counselling is entirely appropriate for those serious disorders that are neither treatable nor preventable. However, genomic tests are being developed for an increasing number of applications (as described above) that do not follow this established paradigm. Indeed the PHG Foundation has recently explored the impact of testing for common variants conferring a very small increased risk of cancer as part of the COGS project. Such tests could be developed as an adjunct to targeting screening interventions in the future, and it is feasible that these could proceed on a self testing basis. Our work suggests that identifying these genetic variants in isolation would not create a sufficiently large increase in risk to justify counselling by medical practitioners. Indeed, we regard such counselling as being counterproductive in that it could increase anxiety and cause psychological harm. In practice, it seems likely that as a preliminary to screening, a broad consent might be sought involving a variety of relevantly trained

professionals (including screening personnel who will not necessarily be medically trained).

25. As noted in paragraph 9 above, in the UK there are a number of companies offering genetic testing on a direct-to-consumer basis. These tests are accessed via the internet, and the consumer is sent a kit to provide a buccal cell or saliva sample which is then analysed. In the UK it is lawful to access these tests, although a voluntary framework has been adopted by the various stakeholders, which suggests that protections are put in place commensurate with the risks associated with various categories of test. We support this framework, and oppose regulations making access to direct-to-consumer genetic tests illegal, on the basis that such regulations seem to be disproportionate, excessive, and demonstrate genetic exceptionalism. Only a small proportion of these tests are diagnostic or predictive tests for inherited conditions, which have well-established clinical validity and clinical utility. We agree that this subset of tests should be offered under the supervision of a medical professional, with appropriate counselling. The correct approach in our view is to work with providers of direct-to-consumer tests to ensure that their practice is consistent with this framework.

Instructions for self-testing devices (ENVI Amendment 350, IMCO Amendment 44)

26. Specific provision for general safety and performance requirements are included at IVDDR Annex 1, paragraph 16 (protection against risks) and 17.3 (Instructions for use). Paragraph 17.3.1.(ii) requires that the instructions contain details of the device's intended use and function (*i.e.* screening, monitoring, diagnosis or aid to diagnosis). In practice these distinctions between screening and diagnosis may be very difficult to make and will depend on the context of use. Amendment 350 adds prognosis and companion diagnostic to these categories. As we have previously stated this requirement could therefore create barriers to implementation by manufacturers without additional guidance.

Direct-to-consumer tests (ENVI Amendment 110 and ENVI Amendment 111)

27. These proposed amendments fetter national laws in two ways: they outlaw the advertising of prescription devices and require that all Class D and certain Class C devices (devices for genetic testing, and companion diagnostics) are only available via medical prescription. If the definition and scope of 'genetic tests' are widened in accordance with amendments described above (e.g. ENVI 18,30, 120 and IMCO 5) we believe that these safeguards are disproportionate.

The evidence base for clinical evaluation (ENVI Amendment 350, IMCO Amendment 44)

28. This proposed amendment impacts upon the breadth of the evidence base for clinical evaluation which is defined in IVDDR Annex XII paragraph 1.2.2.3 and Annex XII paragraph 2.1 as comprising several sources of evidence including "experience of routine diagnostic testing". We are concerned that this evidence base is unduly restrictive and that it excludes relevant evidence such as significant experience of predictive genetic tests, or experience of non-routine tests, which may be relevant in the context of rare diseases for example. Moreover if the scope of the regulation is expanded to include prognostic tests, the evidence base should be similarly expanded. This mismatch between the scope of the regulation and the existing evidence basis could result in an obligation to generate unnecessary clinical performance data.

Clinical utility (ENVI Amendment 127)

29. The extent to which a device provides clinical utility is an important test criterion and manufacturers should be required to provide this data where appropriate. The definition in proposed amendment 127 does not use the customary definition commonly used in relation to genetic tests, which defines clinical utility in terms of the use of an assay, for a particular condition within a defined population.

Clinical performance studies on incapacitated subjects (ENVI Amendment 73-74)

30. The requirement that all conditions be met in Amendments 73 (incapacitated adults) and Amendment 74 (incompetent minors) will mean that certain types of clinical performance study will be impossible, such as studies of emergency treatment in intensive care settings, where interventions have to be made urgently and time is of the essence. In such circumstances, it is unlikely that the conditions set out in these amendments can be satisfied. It seems invidious that these vulnerable groups (such as incompetent adults and minors) could be denied the technological advances that are available to other types of participant as a result of the additional protections that are put in place to safeguard their vulnerability.
31. Similarly, the requirement to 'constantly observe' the degree of distress caused by a clinical performance study, could itself be intrusive and distressing and cause more harm than benefit.

These comments are intended to be helpful. Should you require any further input or explanation from us, please do not hesitate to contact us.

PHG Foundation

5 June 2013

Contact details: alison.hall@phgfoundation.org
ron.zimmern@phgfoundation.org
mark.kroese@phgfoundation.org

Appendix 1

Schedule of Amendments

Committee on the Environment, Public Health and Food Safety (ENVI)

Rapporteur: Peter Liese

ENVI Amendment 4

Proposal for a regulation

Recital 44 a (new)

Text proposed by the Commission

Amendment

(44a) Interventional clinical performance studies and other clinical performance studies involving risk for the subject should only be allowed after assessment and approval by an ethics committee.

Or. en

Justification

Linked to the debate on the clinical trials regulation the rapporteur considers that the role of the ethic committee needs to be strengthened.

ENVI Amendment 6

Proposal for a regulation

Recital 59

Text proposed by the Commission

Amendment

(59) This Regulation respects the fundamental rights and observes the principles recognised in particular by the Charter of Fundamental Rights of the European Union and notably human dignity, the integrity of the person, the protection of personal data, the freedom of art and science, the freedom to conduct business and the right to property. This Regulation should be applied by the Member States in accordance with those rights and principles.

(59) This Regulation respects the fundamental rights and observes the principles recognized in particular by the Charter of Fundamental Rights of the European Union and notably human dignity, the integrity of the person, ***the principle of free and informed consent of the person concerned***, the protection of personal data, the freedom of art and science, the freedom to conduct business and the right to property, ***as well as the Convention on Human Rights and Biomedicine as well as the Additional Protocol to that Convention concerning Genetic Testing for Health Purposes***. This Regulation should be applied by the Member States in accordance with those rights and principles.

Justification

The principle of free and informed consent is a key point in the Charta, Article 3 and should be mentioned here.

ENVI Amendment 7**Proposal for a regulation
Recital 59 a (new)**

Text proposed by the Commission

Amendment

(59a) The principle of informed consent, which is one of the key points of the Charter of Fundamental Rights and certain documents of international organisations such as the Council of Europe and the Organisation for Economic Co-operation and Development (OECD), should be respected in this Regulation. The quality of the in vitro medical devices as well as the framework of their application are crucial, especially with regard to DNA tests. A chapter of informed consent therefore needs to be introduced.

Justification

Linked to Amendment 31. The principle of free and informed consent is a key point in the Charta Article 3 and provisions to respect it should be included in the regulation.

ENVI Amendment 14**Proposal for a regulation
Article 2 - point 1**

Text proposed by the Commission

Amendment

(1) 'medical device' means any instrument, apparatus, appliance, software, implant, reagent, material or other article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific medical purposes of:

- diagnosis, prevention, monitoring,

(1) 'medical device' means any instrument, apparatus, appliance, software, implant, reagent, material or other article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific ***direct or indirect*** medical purposes of:

- diagnosis, prevention, monitoring,

treatment or alleviation of disease,

- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or disability,
- investigation, replacement or modification of the anatomy or of a physiological process or state,
- control or support of conception,
- disinfection or sterilisation of any of the above-mentioned products,

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means.

prediction, treatment or alleviation of disease,

- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or disability,
- investigation, replacement or modification of the anatomy or of a physiological process or state,
- control or support of conception,
- disinfection or sterilisation of any of the above-mentioned products,

- providing information concerning direct or indirect impacts on health,

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means.

Or. en

Justification

a) In Article 2(2), the definition of an in vitro diagnostic medical device has been extended to cover predictive and predisposition testing. However, the definition of a medical device has not been similarly extended. b) So called lifestyle-tests should fall under the regulation as they could have enormous consequences for the health of the patient/consumer. An extended scope therefore is important for protection of patients and consumer in Europe.

ENVI Amendment 16

Proposal for a regulation

Article 2 - point 2 - subparagraph 2 a (new)

Text proposed by the Commission

Amendment

In vitro diagnostic medical devices used for DNA-testing shall be subject to this Regulation.

Or. en

Justification

So called lifestyle-tests should fall under the regulation as they could have enormous consequences for the health of the patient/consumer. An extended scope therefore is important for protection of patients and consumer in Europe.

ENVI Amendment 18

Proposal for a regulation Article 2 - point 12 a (new)

Text proposed by the Commission

Amendment

(12a) 'genetic test' means a test that is carried out for health purposes, involving analysis of biological samples of human origin and aimed specifically at identifying the genetic characteristics of a person which are inherited or acquired during early prenatal development;

Or. en

Justification

The rapporteur introduces specific provisions for genetic tests. That it is why a definition is necessary. The wording is based on the protocol of the Council of Europe.

ENVI Amendment 20

Proposal for a regulation Article 2 - point 21

Text proposed by the Commission

Amendment

(21) 'health institution' means an organisation whose primary purpose is the care or treatment of patients or the promotion of public health;

(21) 'health institution' means an organisation whose primary purpose is the care or treatment of patients or the promotion of public health; ***excluding commercial clinical service labs;***

Or. en

Justification

The regulation foresees some exceptions to meet the needs of hospitals and other healthcare institutions. It should be clarified that commercial labs do not fall under this division because they should not benefit from the same derogations.

ENVI Amendment 30

Proposal for a regulation Article 4 a (new)

Text proposed by the Commission

Amendment

Article 4a

Genetic information, counselling and free consent

1. A device may only be used for the purpose of a genetic test if that test is conducted by persons admitted to the medical profession under the applicable national legislation.

2. A product may only be used for the purposes of a genetic test if the rights, safety and well-being of the test subjects are protected and the clinical data generated in the course of the testing are expected to be reliable and robust.

3. Before using a device for the purpose of a genetic test the person referred to in paragraph 1 shall provide the test subject concerned with appropriate information on the nature, the significance and the implications of the genetic test.

4. Before using a device for the purpose of a genetic test the person referred to in paragraph 1 shall provide the test subject concerned with appropriate and comprehensible genetic counselling without prejudging the outcome. The genetic counselling shall include medical, ethical, social, psychological and legal aspects.

The form and extent of that genetic counselling shall be defined according to the implications of the results of the test and their significance for the person or the members of that person's family, including possible implications concerning procreation choices.

5. A device may only be used for the purpose of a genetic test after the test subject concerned has given free and informed consent to it. That consent shall be given explicitly in writing. The consent may be revoked at any time in writing or orally.

In the case of minors, the informed consent of the parents or legal representative shall be obtained. That consent shall represent the minor's presumed will and may be revoked at any time, without detriment to the minor. In the case of incapacitated adults who are unable to give informed legal consent, the informed consent of the legal representative shall be obtained. The consent shall represent the presumed will of the person concerned and may be

revoked at any time, without detriment to that person.

6. A device may only be used for the determination of gender in connection with prenatal diagnosis, if the determination fulfils a medical purpose and if there is a risk of serious gender specific hereditary diseases. By way of derogation from Article 2(1) and (2) the same restriction on use shall apply to products which are not intended to fulfil a specific medical purpose.

7. The provisions of this Article on the use of devices for the purpose of genetic tests shall not prevent Member States from maintaining or introducing for reasons of health protection or public order more stringent national legislation in this field.

Or. en

Justification

See also Explanatory statement. This new chapter refers to long-standing requests of the European Parliament and other international institutions like the Council of Europe and OECD. Genetic Tests should be performed by a medical professional after appropriate genetic counselling. Informed consent is a prerogative of the Charta of Fundamental Rights and should therefore be introduced in the legislation.

ENVI Amendment 53

Proposal for a regulation Article 49 - paragraph 6 b (new)

Text proposed by the Commission

Amendment

6b. Approval may only be granted if an independent ethics committee has previously submitted a positive evaluation of the clinical performance study. The statement of the ethics committee shall cover, in particular, the medical justification for the study, the consent of the test subject following the provision of full information about the performance study and the suitability of the investigators and investigative facilities.

The ethics committee shall serve to protect the rights, safety and well-being of all test subjects, users and

third parties. The committee shall be independent of the researcher, the sponsor and any other undue influence. It shall take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards. The ethics committee shall be made up of an appropriate number of members, who together are in possession of the relevant qualifications and experience in order to be able to assess the scientific, medical and ethical aspects of the clinical investigation under scrutiny.

Member States shall take the measures necessary to set up ethics committees and to facilitate their work.

Or. en

Justification

Paragraph 6b (new) Subparagraphs 1 and 2 are linked to the debate on ClinicalTrials. The guarantee the protection of the subject, it is necessary to make approval by Member States dependent upon the decision of the competent, independent, interdisciplinary ethics committee. A negative decision by an ethics committee must result in the denial of approval for a clinical performance study. The proposal reflects international protection standards, as set out in the Declaration of Helsinki.

ENVI Amendment 73

**Proposal for a regulation
Annex XII - Part A - point 2.3 a (new)**

Text proposed by the Commission

Amendment

2.3a Clinical performance study on incapacitated subjects

In the case of incapacitated subjects who have not given, or who have not refused to give, informed consent before the onset of their incapacity, clinical performance studies may be conducted only where, in addition to the general conditions, all of the following conditions are met:

- the informed consent of the legal representative has been obtained which represents the subject's presumed will and may be revoked at

any time, without detriment to the subject;

- the incapacitated subject has received adequate information in relation to that person's capacity for understanding regarding the study and its risks and benefits;

- the explicit wish of an incapacitated subject who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical performance study at any time is duly taken into consideration by the investigator;

- no incentives or financial inducements are given other than compensation for participation in the clinical performance study;

- such research is essential to validate data obtained in a clinical performance study on persons able to give informed consent or by other research methods;

- such research relates directly to a life-threatening or debilitating medical condition from which the subject suffers;

- the clinical performance study has been designed to minimise pain, discomfort, fear, and any other foreseeable risk in relation to the disease and developmental stage and both the risk threshold and the degree of distress are specially defined and constantly observed;

- there are grounds for expecting that participation in the Clinical performance study will produce a benefit to the incapacitated subject outweighing the risks or will produce no risk at all;

- an ethics committee, with expertise regarding the relevant disease and the patient population concerned, or that has taken advice on clinical, ethical and psychosocial questions in the field of the relevant disease and patient population concerned, has endorsed the protocol;

The test subject shall as far as possible

take part in the consent procedure.

Or. en

Justification

Compared to the proposal on clinical trials for medicinal products the provisions on interventional clinical performance studies are very weak and imprecise. Interventional clinical performance studies may include a very significant risk for the patient, for example if the specimen is collected by spinal tap. Therefore the provisions need to be specified. The proposal seeks to maintain at least the standard of protection which is guaranteed for clinical trials with medicinal products since 2001 through Directive 2001/20 EC.

ENVI Amendment 74

**Proposal for a regulation
Annex XII - point 2.3 b (new)**

Text proposed by the Commission

Amendment

2.3 b Clinical performance study on minors

A Clinical performance study on minors may be conducted only where, in addition to the general conditions, all of the following conditions are met:

- the informed consent of the legal representative has been obtained, whereby consent shall represent the minor's presumed will;***
- the minor has received all relevant information in a way adapted to the minor's age and maturity, from a medical doctor (either the investigator or member of the study team) trained or experienced in working with children, regarding the trial, the risks and the benefits;***
- the explicit wish of a minor who is capable of forming an opinion and assessing the information referred to above to refuse participation in, or to be withdrawn from, the clinical performance study at any time, is duly taken into consideration by the investigator;***
- no incentives or financial inducements are given other than compensation for participation in the clinical performance study***

- such research is essential to validate data obtained in clinical performance studies on persons able to give informed consent or by other research methods;

- such research either relates directly to a medical condition from which the minor concerned suffers or is of such a nature that it can only be carried out on minors;

- the clinical performance study has been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage, and both the risk threshold and the degree of distress are specially defined and constantly observed;

- some direct benefit for the group of patients is obtained from the clinical performance study;

- the corresponding scientific guidelines of the Agency have been followed;

- an ethics committee, with paediatric expertise or after taking advice in clinical, ethical and psychosocial problems in the field of paediatrics, has endorsed the protocol.

The minor shall take part in the consent procedure in a manner adapted to his or her age and maturity.

Or. en

Justification

Compared to the proposal on clinical trials for medicinal products the provisions on interventional clinical performance studies are very weak and imprecise. Interventional clinical performance studies may include a very significant risk for the patient, for example if the specimen is collected by spinal tap. Therefore the provisions need to be specified. The proposal seeks to maintain at least the standard of protection which is guaranteed for clinical trials with medicinal products since 2001 through Directive 2001/20 EC.

Proposal for a regulation
Recital 9

Text proposed by the Commission

(9) To ensure the highest level of health protection, the rules governing in vitro diagnostic medical devices manufactured and used, ***including measurement and delivery of results***, only within a single ***health institution*** should be clarified and strengthened.

Amendment

(9) To ensure the highest level of health protection, the rules governing in vitro diagnostic medical devices manufactured and used only within a single ***site*** should be clarified and strengthened.

Or. en

Justification

The words health institution have been excised - since health institutions will be exempt from the Regulation, then the target of this recital is actually the commercial laboratories which will not be exempt.

ENVI Amendment 83
Rebecca Taylor, Linda McAvan, Marina Yannakoudakis

Proposal for a regulation
Recital 9 a (new)

Text proposed by the Commission

Amendment

(9a) In the case of urgent or unmet medical needs for patients, such as emerging pathogens and rare diseases, single health institutions should have the possibility to manufacture, modify and use devices in-house and therefore address, within a non-commercial and flexible framework, specific needs which cannot be met by an available CE-marked device.

Or. en

Justification

The proposal removes the possibility of health institutions producing or modifying class D devices. There are patient needs for which there are no commercially available IVD Devices, such as the diagnosis of very rare diseases, or the identification of emerging pathogens. Health institutions play a vital role in protecting public health, by manufacturing these devices in-house. These amendments seek to maintain this public health function whilst ensuring patient safety is paramount.

ENVI Amendment 100
Dagmar Roth-Behrendt

Proposal for a regulation
Recital 44 a (new)

Text proposed by the Commission

Amendment

(44a) An interventional clinical performance studies or any other clinical performance study should only start after being granted a positive evaluation by an independent ethics committee. Member States should take the necessary measures to establish Ethics Committees where such committees do not exist.

ENVI Amendment 110
Margrete Auken

Proposal for a regulation
Article 1 - paragraph 6

Text proposed by the Commission

Amendment

6. This Regulation shall not affect national laws which require that certain devices may only be supplied on a medical prescription.

6. This Regulation shall not affect national laws which require that certain devices may only be supplied on a medical prescription. ***Direct to consumer advertising of devices classed as prescription only by this regulation shall be illegal.***

The following devices may only be supplied on a medical prescription:

1) Class D devices

2) Class C devices in the following categories:

(a). devices for genetic testing;

(b). companion diagnostics.

The Commission shall be empowered to adopt delegated acts in accordance with Article 85 to decide on self-testing devices and other category C tests after consultation with stakeholders.

Or. en

ENVI Amendment 111

Peter Liese, Christel Schaldemose, Alda Sousa, Paolo Bartolozzi, Anne Delvaux, Anna Rosbach, Thomas Ulmer, Zofija Mazej Kukovič, Renate Sommer, Mairead McGuinness, Richard Seeber, Miroslav Mikolášik

Proposal for a regulation

Article 1 - paragraph 6

Text proposed by the Commission

6. This Regulation shall not affect national laws which require that certain devices may only be supplied on a medical prescription.

Amendment

6. This Regulation ***requires that certain devices may only be supplied on a medical prescription but*** shall not affect national laws which require that certain ***other*** devices may also only be supplied on a medical prescription. ***Direct to consumer advertising of devices classed as prescription only by this regulation shall be illegal.***

The following devices may only be supplied on a medical prescription:

1) Class D devices

2) Class C devices in the following categories:

(a) devices for genetic testing;

(b) companion diagnostics.

The Commission shall be empowered to adopt delegated acts in accordance with Article 85 to decide on other category C tests after consultation with stakeholders.

Or. en

ENVI Amendment 112

Rebecca Taylor

Proposal for a regulation

Article 2 - paragraph 1 - subparagraph 1 - point 1 - indent 1

Text proposed by the Commission

- diagnosis, prevention, monitoring, treatment or alleviation of disease,

Amendment

- diagnosis, prevention, monitoring, ***prediction, prognosis***, treatment or alleviation of disease,

Or. en

Justification

The prediction and prognosis of diseases are vital functions of devices

ENVI Amendment 117

Alda Sousa

Proposal for a regulation

Article 2 - paragraph 1 - subparagraph 1 - point 6

Text proposed by the Commission

(6) ‘companion diagnostic’ means a device ***specifically*** intended to ***select*** patients ***with a previously diagnosed condition or predisposition as eligible for a targeted therapy***;

Amendment

(6) ‘companion diagnostic’ means a device intended to ***provide information that is essential for the safe and effective use of a corresponding therapeutic product. The use of a companion diagnostic with a particular therapeutic product is indicated as desirable in the instructions for use in the labelling of both the diagnostic device and the corresponding therapeutic product, as well as in the labelling of any generic equivalents of the therapeutic product or is the stated intended purpose of the diagnostic device.***

An IVD companion diagnostic device could be essential for the safe and effective use of a corresponding therapeutic product to:

- identify patients who are most likely to benefit from a particular therapeutic product;

- identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product;

- monitor response to treatment for the purpose of adjusting treatment (e.g. schedule, dose, discontinuation) to achieve improved safety or effectiveness.

Or. en

Justification

The current definition is too limited, e.g. it does not include companion diagnostics used to guide dosage decisions (e.g. pharmacogenetic tests for warfarin treatment) which may

have an important role to play in ensuring the safety and effectiveness of a specific drug.

ENVI Amendment 120

Peter Liese, Christel Schaldemose, Alda Sousa, Margrete Auken, Paolo Bartolozzi, Anne Delvaux, Anna Rosbach, Thomas Ulmer, Zofija Mazej Kukovič, Renate Sommer, Mairead McGuinness, Richard Seeber, Nora Berra, Miroslav Mikolášik

Proposal for a regulation

Article 2 - paragraph 1 - subparagraph 1 - point 12 a (new)

Text proposed by the Commission

Amendment

(12a) ‘ device for genetic testing’ means an in vitro diagnostic medical device the purpose of which is to identify a genetic characteristic of a person which is inherited or acquired during prenatal development.

Or. en

Justification

Other definition compared to Amendment 18 in the draft report

ENVI Amendment 127

Alda Sousa

Proposal for a regulation

Article 2 - paragraph 1 - subparagraph 5 - point 32 b (new)

Text proposed by the Commission

Amendment

(32b) ‘clinical utility’ means the anticipated effect(s) of the clinical use of the test result, including on health outcomes, where the intended purpose of a device, as stated by the manufacturer, includes a clinical use such as selection of a therapy (e.g. companion diagnostic);

Or. en

ENVI Amendment 141

Rebecca Taylor, Linda McAvan, Marina Yannakoudakis

Proposal for a regulation

Article 4 - paragraph 5 - subparagraph 2

Text proposed by the Commission

Amendment

Devices classified as class D in accordance with the rules set out in Annex VII, **even** if manufactured and used

Devices classified as class D in accordance with the rules set out in Annex VII, if manufactured and used within a single

within a single health institution, shall **comply with** the requirements of this Regulation. **However, the provisions regarding CE marking set out in Article 16 and the obligations referred to in Articles 21 to 25 shall not apply to those devices.**

health institution, shall **be exempt from** the requirements of this Regulation, **with the exception of Article 59(4), where the following conditions are met;**

(a) the recipient patient or patient group's specific needs can not be met by an available CE-marked device;

(b) the health institution is accredited to EN ISO standard 15189 quality management system, or any other equivalent recognised standard;

(c) the health institution provides their competent authority referred to in Article 26 with a list of such devices, which shall include a justification of their manufacturing or modification, in particular, where similar devices have been made available on the market. This information shall be updated yearly, and shall be made public.

Or. en

Justification

The proposal removes the possibility of health institutions producing or modifying class D devices. There are patient needs for which there are no commercially available IVD Devices, such as the diagnosis of very rare diseases, or the identification of emerging pathogens. Health institutions play a vital role in protecting public health, by manufacturing these devices in-house. These amendments seek to maintain this public health function whilst ensuring patient safety is paramount.

ENVI Amendment 142

Rebecca Taylor, Linda McAvan, Marina Yannakoudakis

Proposal for a regulation

Article 4 - paragraph 5 a (new)

Text proposed by the Commission

Amendment

5a. Member States shall retain the right to restrict the in-house manufacture and use of any specific type of in-vitro diagnostic device in relation to aspects that are not covered by this Regulation, and may also make the manufacture and use of the devices concerned subject to further safety requirements.

Justification

The proposal removes the possibility of health institutions producing or modifying class D devices. There are patient needs for which there are no commercially available IVD Devices, such as the diagnosis of very rare diseases, or the identification of emerging pathogens. Health institutions play a vital role in protecting public health, by manufacturing these devices in-house. These amendments seek to maintain this public health function whilst ensuring patient safety is paramount.

ENVI Amendment 144

Peter Liese, Christel Schaldemose, Alda Sousa, Margrete Auken, Paolo Bartolozzi, Anne Delvaux, Anna Rosbach, Thomas Ulmer, Zofija Mazej Kukovič, Renate Sommer, Mairead McGuinness, Richard Seeber, Miroslav Mikolášik

Proposal for a regulation Article 4 a (new)

Text proposed by the Commission

Amendment

Article 4a

- 1. A device may only be used for the purpose of a genetic test if the indication is given by persons admitted to the medical profession under the applicable national legislation after a personal consultation.**
- 2. A device may be used for purposes of a genetic test only in a way that the rights, safety and well-being of the subjects are protected and that the clinical data generated in the course of the genetic testing are going to be reliable and robust.**
- 3. Information. Before using a device for the purpose of a genetic test the person mentioned in paragraph 1 shall provide the person concerned with appropriate information on the nature, the significance and the implications of the genetic test.**
- 4. Genetic counselling. Appropriate genetic counselling is mandatory before using a device for the purpose of predictive and prenatal testing and after a genetic condition has been diagnosed. It shall include medical, ethical, social, psychological and legal aspects and has to be addressed by physicians qualified in genetic counselling.**

The form and extent of this genetic counselling shall be defined according to the implications of the results of the test and their significance for the person or the members of his or her family, including possible implications concerning procreation choices.

5. Consent. A device may only be used for the purpose of a genetic test after the person concerned has given free and informed consent to it. The consent has to be given explicitly and in writing. It can be revoked at any time in writing or orally.

6. Testing of minors. In case of minors the informed consent of the parents or legal representative shall be obtained; consent must represent the minor's presumed will and may be revoked at any time, without detriment to the minor. In case of incapacitated adults not able to give informed legal consent, the informed consent of the legal representative shall be obtained; consent must represent the presumed will and may be revoked at any time, without detriment to the person.

Devices predicting a genetic condition that has implications for diseases in adulthood or for family planning shall not be used in minors unless preventive means are available before reaching the age when the person tested is able to give consent.

7. A device may only be used for the determination of sex in connection with prenatal diagnosis, if the determination fulfils a medical purpose and if there is a risk of serious gender specific hereditary diseases. By way of derogation of Article 2(1) and (2) this also applies to products which are not intended to fulfil a specific medical purpose.

8. The provisions of this Article on the use of devices for the purpose of genetic tests do not prevent the Member States from maintaining or introducing for reasons of health protection or public order more stringent national legislation in this field.

Justification

New element in paragraph 5 compared to the wording in the draft report (Amendment 30). This amendment clarifies also the purpose of Article 4a paragraph 4 after consultation with the shadows and experts. It needs to be made clear that genetic counselling is not mandatory when it just confirms a specific diagnosis and it is also not necessary for companion diagnostics or when the genetic test shows a normal finding.

ENVI Amendment 244
Dagmar Roth-Behrendt

Proposal for a regulation
Chapter 5 - Section 1 a - Article 39 c (new)

Text proposed by the Commission

Amendment

Article 39 c (new)

Centralised procedure

- 1. A Committee for the Authorisation of In Vitro Diagnostic Medical Devices is hereby established in accordance with the provisions of Article 39d. The Committee shall be part of the European Medicines Agency.**
- 2. The Committee for the Authorisation of In Vitro Diagnostic Medical Devices shall be responsible for drawing up the opinion of the Agency on any matter concerning the admissibility of applications submitted in accordance with the centralised procedure, the granting, variation, suspension or revocation of an authorisation to place class D devices on the market.**
- 3. Each application for the devices referred to in Article 39a (1) shall include the particulars and documents as referred to in Annexes VII, IX and X, as relevant.**
- 4. The application shall be accompanied by the fee payable to the Agency for examining the application.**
- 5. The Agency shall ensure that the opinion of the Committee for the Authorisation of In Vitro Diagnostic Medical Devices is issued within 210 days from receipt of a valid application.**

The Committee for the Authorisation of Medical Devices shall be given at least 80 days from receipt of an application for analysing the scientific data in the documentation accompanying an application for a marketing authorisation. On the basis of a duly reasoned request, from the Committee for the Authorisation of In Vitro Diagnostic Medical Devices, the Agency may extend that period.

6. The Committee may only once request the manufacturer to submit additional information that for scientifically valid grounds is necessary for the assessment of the application for marketing authorisation. This may include a request for samples or an on-site visit to the manufacturer's premises. Where such a request has been made, the period referred to in paragraph 5 shall be suspended until the additional information requested has been supplied.

7. The Commission shall, in consultation with the Agency, the Member States and interested parties, draw up a detailed guide concerning the form in which applications for authorisation are to be presented.

8. Where the Committee for the Authorisation of In Vitro Diagnostic Medical Devices considers it necessary in order to complete its examination of an application, it may require the applicant to undergo a specific inspection of the manufacturing site of the device concerned. Such inspections shall be made unannounced.

The inspection shall be carried out within the time-limit laid down in paragraph 5 by inspectors from the Member State holding the appropriate qualifications. Those inspectors may be accompanied by a rapporteur or an expert appointed by the Committee for the Authorisation of In Vitro Diagnostic Medical Devices.

9. The Agency shall forthwith inform the applicant if the opinion of the Committee for the Authorisation of In Vitro Diagnostic Medical Devices is

that:

(a) the application does not satisfy the criteria for authorisation set out in this Regulation;

(b) the documentation accompanying the application is not in compliance with the provisions of this Regulation or needs to be amended or supplemented;

(c) the marketing authorisation needs to be granted subject to certain conditions.

(d) the marketing authorisation for the medical device concerned needs to be refused on grounds that the device does not comply with this Regulation.

10. Within 15 days of receipt of the opinion referred to in paragraph 9, the applicant may notify the Agency in writing of his intention to request a re-examination of the opinion. In such a case, the applicant shall transmit to the Agency the detailed grounds for such a request within 60 days of receipt of the opinion.

Within 60 days following receipt of the grounds for the request, the Committee for the Authorisation of In Vitro Diagnostic Medical Devices shall re-examine its opinion in accordance with the conditions laid down in the fourth subparagraph of Article 62(1) of Regulation (EC) 726/2004. The reasons for the conclusion reached shall be annexed to the final opinion.

11. Within 15 days from its adoption, the Agency shall send the final opinion of the Committee for the Authorisation of In Vitro Diagnostic Medical Devices to the Commission, the Member States and the applicant, together with a report describing the assessment of the device by the Committee for the Authorisation of In Vitro Diagnostic Medical Devices and stating the reasons for its conclusions.

12. If an applicant withdraws an application for a marketing authorisation submitted to the Agency before an opinion has been issued concerning that application, the

applicant shall communicate its reasons for withdrawal to the Agency. The Agency shall make this information publicly available and shall publish the assessment report, if available, after deleting all information of a commercially confidential nature.

13. Within 15 days of receipt of the opinion referred to in paragraph 11, the Commission shall prepare a draft of the decision to be taken in respect of the application.

Where the draft decision diverges from the opinion of the Agency, the Commission shall annex a detailed explanation of the reasons for the differences.

The draft decision shall be transmitted to the Member States and the applicant.

Member States shall have 22 days to submit their written observations on the draft decision to the Commission. However, if a decision has to be taken urgently, a shorter time-limit may be set by the Chairperson of the Committee for the Authorisation of In Vitro Diagnostic Medical Devices according to the degree of urgency involved. This time-limit shall not, otherwise than in exceptional circumstances, be shorter than 5 days;

14. Member States may request in writing that the draft decision referred to in paragraph 13 be discussed by a plenary meeting of the Committee for the Authorisation of In Vitro Diagnostic Medical Devices, stating their reasons in detail.

Where, in the opinion of the Commission, a Member State's written observations raise important new questions of a scientific or technical nature which the opinion delivered by the Agency has not addressed, the Chairperson of the Committee for the Authorisation of In Vitro Diagnostic Medical Devices shall suspend the procedure and refer the application back to the Agency for further consideration.

15. The Commission shall take a final decision within 30 days from the end of the examination procedure referred to in Article 84(3).

16. The refusal of a marketing authorisation shall constitute a prohibition on the placing on the market of the devices referred to in Article 39a(1) throughout the Union.

17. After a marketing authorisation has been granted, the marketing authorisation holder shall inform the Agency of the dates of actual placing on the market of the device in the Member States, taking into account the various presentations authorised.

18. The marketing authorisation holder shall also notify the Agency if the product ceases to be placed on the market, either temporarily or permanently, and it shall provide a justification on medical and/or economic grounds in this respect.

Or. en

ENVI Amendment 245
Dagmar Roth-Behrendt

Proposal for a regulation
Chapter 5 - Section 1 a - Article 39 d (new)

Text proposed by the Commission

Amendment

Article 39d

Committee for the Authorisation of In Vitro Diagnostic Medical Devices

1. The Committee for the Authorisation of In Vitro Diagnostic Medical Devices shall be composed of the following:

(a) one member and one alternate member appointed by each Member State, in accordance with paragraph 3 of this Article;

(b) six members appointed by the Commission, with a view to ensuring that the relevant expertise in the field of medical devices is available within the Committee, on the basis of a public call for expressions of interest;

(c) one member and one alternate member appointed by the Commission, on the basis of a public call for expressions of interest, after consulting the European Parliament, in order to represent healthcare professionals;

(d) one member and one alternate member appointed by the Commission, on the basis of a public call for expressions of interest, after consulting the European Parliament, in order to represent patient organisations.

The alternate members shall represent and vote for the members in their absence. The alternate members referred to in point (a) may be appointed to act as rapporteurs in accordance with Article 62 of Regulation (EC) 726/2004.

2. A Member State may delegate its tasks in the Committee for the Authorisation of In Vitro Diagnostic Medical Devices to another Member State. Each Member State may represent no more than one other Member State.

3. The members and alternate members of Committee for the Authorisation of In Vitro Diagnostic Medical Devices shall be appointed on the basis of their relevant expertise in the field of in vitro diagnostic medical devices, in order to guarantee the highest levels of specialist qualifications and a broad spectrum of relevant expertise. For this purpose, Member States shall liaise with the Management Board of the Agency and the Commission in order to ensure that the final composition of the Committee for the Authorisation of In Vitro Diagnostic Medical Devices covers the scientific areas relevant to its tasks.

4. The members and alternate members of the Committee for the Authorisation of In Vitro Diagnostic Medical Devices shall be appointed for a term of three years, which may be prolonged once and thereafter renewed following the procedures referred to in paragraph 1. The Committee shall elect its

Chairperson from among its full members for a term of three years, which may be prolonged once.

5. Paragraphs 3, 4, 5, 6, 7 and 8 of Article 61 of Regulation (EC) 726/2004 shall apply to the Committee for the Authorisation of In Vitro Diagnostic Medical Devices.

6. The mandate of the Committee for the Authorisation of In Vitro Diagnostic Medical Devices shall cover all aspects of the evaluation of medical devices in the scope of the procedures under Articles 39c and 39f ;

**ENVI Amendment 280
Dagmar Roth-Behrendt**

**Proposal for a regulation
Article 48 a (new)**

Text proposed by the Commission

Amendment

Article 48 a

Involvement of Ethics Committee

1. Authorisation to conduct a clinical performance study may only be granted if an independent ethics committee has previously submitted a positive evaluation of that performance study.

2. The statement of the Ethics Committee shall cover in particular the medical justification, the consent of the test subjects participating in the clinical performance study following the provision of full information about the clinical performance study and the suitability of the investigators and investigation facilities.

3. The Ethics Committee shall ensure that the rights, safety and well-being of subjects participating in a clinical performance study are protected.

4. It shall be independent of the researcher, independent of the sponsor, and free of any other undue influence. It shall act in accordance with the laws and regulations of the country or countries in which the

research is to be conducted and must abide by all relevant international norms and standards.

5. The Ethics Committee shall consist of a clearly defined number of members and substitutes which include healthcare professionals, laypersons and at least one well-experienced, knowledgeable patient or patient representative, who collectively possess the relevant qualifications and experience to be able to review and evaluate the scientific, medical and ethical aspects of the proposed clinical performance study.

6. Member States shall take the necessary measures to establish Ethics Committees where such committees do not exist, and to facilitate their work.

Members States shall publish the number, the names and the professions of the members and substitutes of the Ethics Committees and inform the Commission about the composition of the Ethics Committees and the date on which they become operational.

Or. en

ENVI Amendment 345
Alda Sousa

Proposal for a regulation
Annex 1 - part II - point 6 - point 6.1 - point b

Text proposed by the Commission

(b) the clinical performance, such as diagnostic sensitivity, diagnostic specificity, positive and negative predictive value, likelihood ratio, expected values in normal or affected populations.

Amendment

(b) the clinical performance, ***including measures of clinical validity*** such as diagnostic sensitivity, diagnostic specificity, positive and negative predictive value, likelihood ratio, expected values in normal or affected populations; ***and, where appropriate, measures of clinical utility. In the case of companion diagnostics, evidence of the clinical utility of the device for the intended purpose (selection of patients with a previously diagnosed condition or predisposition eligible for a targeted therapy) is required. For a companion diagnostic, the manufacturer should supply clinical evidence relating to the***

impact of a positive or negative test on (1) patient care; and (2) health outcomes, when used as directed with the stated therapeutic intervention.

ENVI Amendment 347
Margrete Auken
on behalf of the Verts/ALE Group

Proposal for a regulation
Annex 1 - part II - point 16 a (new)

Text proposed by the Commission

Amendment

16 a. The devices intended for self-testing help consumers access information about their health. However, lack of proper counselling regarding the use of self-testing devices - such as the sampling, reading and interpreting results - can lead to traumatic events and may harm users. Therefore, Member States should ensure appropriate counselling conducted by persons admitted to the medical profession under the applicable national legislation before the use of such self-testing devices that are manufactured to test for chronic and transmittable diseases.

Or. en

Justification

Sampling, reading and interpreting results are procedures which allow for faulty handling and defective manoeuvres when they are carried out by lay persons. Self-tests only make sense if they are part of coherent multidisciplinary management of a medical condition. Without proper counselling by doctor, some people may consider that the information made available by the self-testing devices is exact. Proper counselling can also help reduce the possible risk of abuse for example pressure or coercion by a partner or an employer.

ENVI Amendment 350
Alda Sousa

Proposal for a regulation
Annex 1 - part III - point 17 - point 17.3 - point 17.3.1 - point ii - indent 2

Text proposed by the Commission

- its function (e.g. screening, monitoring, diagnosis or aid to diagnosis);

Amendment

- its function (e.g. screening, monitoring, diagnosis or aid to diagnosis, **prognosis, companion diagnostic**);

Or. en

ENVI Amendment 385

Alda Sousa

Proposal for a regulation

Annex 7 - part 1 - point 1.1

Text proposed by the Commission

1.1. Application of the classification rules shall be governed by the intended purpose of the devices.

Amendment

1.1. Application of the classification rules shall be governed by the intended purpose, **novelty, complexity and inherent risk** of the devices.

ENVI Amendment 387

Alda Sousa

Proposal for a regulation

Annex 7 - part 2 - point 2.3 - paragraph 1 - point f - point ii

Text proposed by the Commission

(ii) Devices intended to be used for disease staging; or

Amendment

(ii) Devices intended to be used for disease staging **or prognosis**; or

Or. en

Justification

Disease prognosis is an increasingly common application in the molecular diagnostic sector, exemplified by tests such as Agendia's Mammaprint and Genomic Health's Oncotype Dx, which are both used to give prognostic scores for likelihood of disease recurrence in breast cancer after surgery. Because prognosis is a form of patient selection, we believe that such devices should explicitly be included under Rule 3.

ENVI Amendment 389

Alda Sousa

Proposal for a regulation

Annex 7 - part 2 - point 2.6 - paragraph 1

Text proposed by the Commission

Devices not covered by the above-mentioned classification rules are classified as class B.

Amendment

Devices not covered by the above-mentioned classification rules are classified as class B. ***However, novel class B devices will be classified as class C.***

ENVI Amendment 391

Anna Rosbach

Proposal for a regulation

Annex 8 - section 2 - point 6 - point 6.2 - point c

Text proposed by the Commission

(c) For companion diagnostic intended to be used to assess the patient eligibility to a treatment with a specific medicinal product, the notified body shall consult before issuing an EU design-examination certificate and on the basis of the draft summary of safety and performance and the draft instructions for use, one of the competent authorities designated by the Member States in accordance with Directive 2001/83/EC (hereinafter referred to as ‘medicinal products competent authority’) or the European Medicines Agency (hereinafter referred to as ‘EMA’) established by the Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, regarding the suitability of the device in relation to the medicinal product concerned. Where the medicinal product falls exclusively within the scope of the Annex of Regulation (EC) No 726/2004, the notified body shall consult the EMA.

Amendment

(c) Before issuing an EU design-examination certificate, the notified body shall request a reference laboratory, where designated in accordance with Article 78, to verify compliance of the device with the CTS, when available, or with other solutions chosen by the manufacturer to ensure a level of safety and performance that is at least equivalent. The reference laboratory shall provide a scientific opinion within 30 days. The scientific opinion of the reference laboratory and any possible updates shall be included in the documentation of the notified body concerning the device. The notified body shall give due consideration to the views expressed in the scientific opinion when making its decision. The notified body shall not deliver the certificate if the scientific opinion is unfavourable.

Or. en

Justification

This shifts the consultation process to the development of Common Technical Specifications for companion diagnostics, setting up minimal performance requirements for those tests; these requirements would also be available to the users ensuring a better

transparency of the system. In addition, the consultation of EMA or competent authorities for medicinal products would not be appropriate in regard to the performance of the IVD tests to be used together with the personalized medicine. None of them have the necessary competences and mandate regarding the assessment of the safety and performance of those tests.

ENVI Amendment 392
Anna Rosbach

Proposal for a regulation
Annex 8 - section 2 - point 6 - point 6.2 - point c a (new)

Text proposed by the Commission

Amendment

(c a) Changes to the approved design shall receive further approval from the notified body which issued the EU design-examination certificate, wherever the changes could affect conformity with the general safety and performance requirements of this Regulation or with the conditions prescribed for use of the device. The applicant shall inform the notified body which issued the EU design-examination certificate of any planned changes to the approved design. The notified body shall examine the planned changes, notify the manufacturer of its decision and provide him with a supplement to the EU design-examination report. Where the changes could affect compliance with the CTS or with other solutions chosen by the manufacturer which were approved through the EU design examination certificate, the notified body shall consult the reference laboratory that was involved in the initial consultation, in order to confirm that compliance with the CTS or with other solutions chosen by the manufacturer to ensure a level of safety and performance that is at least equivalent are maintained. The reference laboratory shall provide a scientific opinion within 30 days. The approval of any change to the approved design shall take the form of a supplement to the EU design-examination certificate.

Or. en

Justification

This shifts the consultation process to the development of Common Technical Specifications for companion diagnostics, setting up minimal performance requirements for those tests; these requirements would also be available to the users ensuring a better transparency of the system. In addition, the consultation of EMA or competent authorities for medicinal products would not be appropriate in regard to the performance of the IVD tests to be used together with the personalized medicine. None of them have the necessary competences and mandate regarding the assessment of the safety and performance of those tests.

ENVI Amendment 394

Anna Rosbach

Proposal for a regulation

Annex 9 - point 3 - paragraph 1 - point 3.5

Text proposed by the Commission

3.5. in the case of devices classified as class D, request a reference laboratory, where designated in accordance with Article 78, to verify compliance of the device with the CTS or with other solutions chosen by the manufacturer to ensure a level of safety and performance that is at least equivalent. The reference laboratory shall provide a scientific opinion within 30 days. The scientific opinion of the reference laboratory and any possible update shall be included in the documentation of the notified body concerning the device. The notified body shall give due consideration to the views expressed in the scientific opinion when making its decision. The notified body shall not deliver the certificate if the scientific opinion is unfavourable;

Amendment

3.5. in the case of devices classified as class D, **or for companion diagnostics**, request a reference laboratory, where designated in accordance with Article 78, to verify compliance of the device with the CTS or with other solutions chosen by the manufacturer to ensure a level of safety and performance that is at least equivalent. The reference laboratory shall provide a scientific opinion within 30 days. The scientific opinion of the reference laboratory and any possible update shall be included in the documentation of the notified body concerning the device. The notified body shall give due consideration to the views expressed in the scientific opinion when making its decision. The notified body shall not deliver the certificate if the scientific opinion is unfavourable;

Or. en

Justification

This shifts the consultation process to the development of Common Technical Specifications for companion diagnostics, setting up minimal performance requirements for those tests; these requirements would also be available to the users ensuring a better transparency of the system. In addition, the consultation of EMA or competent authorities for medicinal products would not be appropriate in regard to the performance of the IVD tests to be used together with the personalized medicine. None of them have the necessary competences and mandate regarding the assessment of the safety and performance of those tests.

ENVI Amendment 395
Anna Rosbach

Proposal for a regulation
Annex 9 - point 3 - paragraph 1 - point 3.6

Text proposed by the Commission

Amendment

3.6. For companion diagnostic intended to be used to assess the patient eligibility to a treatment with a specific medicinal product, seek the opinion, on the basis of the draft summary of safety and performance and the draft instructions for use, of a one of the competent authorities designated by the Member States in accordance with Directive 2001/83/EC (hereinafter referred to as ‘medicinal products competent authority’) or the European Medicines Agency (hereinafter referred to as ‘EMA’) on the suitability of the device in relation to the medicinal product concerned. Where the medicinal product falls exclusively within the scope of the Annex of Regulation (EC) No 726/2004, the notified body shall consult the EMA. The medicinal products authority or the European Medicines Agency shall deliver its opinion, if any, within 60 days upon receipt of the valid documentation. This 60-day period may be extended only once for a further 60 days on scientifically valid grounds. The opinion of the medicinal products authority or of the EMA and any possible update shall be included in the documentation of the notified body concerning the device. The notified body shall give due consideration to the opinion, if any, expressed by the medicinal products competent authority concerned or the EMA when making its decision. It shall convey its final decision to the medicinal products competent authority concerned or to the EMA. *deleted*

Or. en

Justification

This shifts the consultation process to the development of Common Technical Specifications for companion diagnostics, setting up minimal performance requirements

for those tests; these requirements would also be available to the users ensuring a better transparency of the system. In addition, the consultation of EMA or competent authorities for medicinal products would not be appropriate in regard to the performance of the IVD tests to be used together with the personalized medicine. None of them have the necessary competences and mandate regarding the assessment of the safety and performance of those tests.

IMCO Amendment 4

Proposal for a regulation Article 2 - point 1 - indent 1

Text proposed by the Commission

- diagnosis, prevention, monitoring, treatment or alleviation of disease,

Amendment

- diagnosis, prevention, **prediction**, monitoring, treatment or alleviation of disease,

Or. en

Justification

It should be clarified that tests which are intended to predict diseases are IVDs and fall within the scope of the IVD regulation. This should apply whether the tests are highly predictive (e.g. a genetic test for Huntington Disease), or only provide information about modest increases in disease risk (as is the case with genetic susceptibility testing for many common diseases).

IMCO Amendment 5

Proposal for a regulation Article 2 - point 3 a (new)

Text proposed by the Commission

Amendment

3a. 'genetic test' means a test that is carried out for health purposes, involving analysis of biological samples of human origin and aiming specifically to identify the genetic characteristics of a person which are inherited or acquired during early prenatal development;

Or. en

Justification

As this regulation contains rules on in vitro diagnostic devices for the purpose of genetic testing, the term 'genetic testing' should be defined.

IMCO Amendment 11

Proposal for a regulation
Article 4 - paragraph 5 - subparagraph 1

Text proposed by the Commission

5. With the exception of Article 59(4), the requirements of this Regulation shall not apply to devices classified as class A, B and C, in accordance with the rules set out in Annex VII, and manufactured and used only within a single health institution, provided manufacture and use occur solely under the health institution's single quality management system, and the health institution is compliant with standard EN ISO 15189 or any other equivalent recognised standard. Member States may require that the health institutions submit to the competent authority a list of such devices which have been manufactured and used on their territory and may make the manufacture and use of the devices concerned subject to further safety requirements.

Amendment

5. With the exception of Article 59(4), the requirements of this Regulation shall not apply to devices classified as class A, B and C, in accordance with the rules set out in Annex VII, and manufactured and used only within a single health institution, provided manufacture and use occur solely under the health institution's single quality management system, and the health institution is compliant with standard EN ISO 15189 or an equivalent recognised standard. ***However, the requirements of this Regulation shall continue to apply to clinical or commercial pathology laboratories which do not have health care (i.e. care and treatment of patients) or the promotion of public health as their primary purpose.*** Member States may require that the health institutions submit to the competent authority a list of such devices which have been manufactured and used on their territory and may make the manufacture and use of the devices concerned subject to further safety requirements.

Or. en

Justification

It should be clear that the exemption only covers institutions that are part of the public healthcare system.

IMCO Amendment 44

Proposal for a regulation
Annex VII - section 2.3 - point f - point iii a (new)

Text proposed by the Commission

Amendment

(iiia) Devices intended to be used for prognosis

Or. en

Justification

Disease prognosis is an increasingly common application in the molecular diagnostic sector, exemplified by tests such as Agendia's Mammaprint and Genomic Health's Oncotype Dx, which are both used to give prognostic scores for likelihood of disease recurrence in breast cancer patients after surgery.

IMCO Amendment 62

Nora Berra

Proposal for a regulation

Article 4 - paragraph 5 - subparagraph 2 a (new)

Text proposed by the Commission

Amendment

In addition, devices classified as class D and required to be used for transfusion or transplantation purposes, when not available as CE marked, or available as CE marked but not reaching the appropriate standards or specifications required by the users, may be manufactured and used within a single health institution without fulfilling the requirements of this Regulation, provided they comply with the conditions defined in the first subparagraph, and the essential requirements (Annex I), and applicable harmonized standards (Article 6), and applicable common technical specifications (Article 7).

Or. en

Justification

For the detection of rare or infrequent transmissible agents where no CE marked are available, "in house" class D devices should be exempted from some requirements of the regulation. However, to demonstrate compliance with state of the art quality and safety requirements these IVDs shall comply with the essential requirements (Annex I), harmonized standards and applicable common technical specifications.