# Response of the German Medical Association

to the proposal by the European Commission
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
(COM(2012)542)

and

for a Regulation of the European Parliament and of the Council
on *in vitro* diagnostic medical devices
(COM(2012)541)

in coordination with
the Standing Conference of Secretary Generals and the Chairpersons of the Ethics Committees of the State Chambers of Physicians

Berlin, 22/02/2013

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# Preliminary Remarks

The EU Commission aims to achieve the following objectives with the proposed Regulation:

- The merging of the Directives on active implantable medical devices (90/385/EEC) and the Directive on medical devices (93/42/EEC)
- A reduction in divergences arising in the interpretation and application of the Directives which have applied until the present time
- The elimination of regulatory loopholes
- A reflection of scientific and technical progress
- An enhancement of the safety level for the manufacture and placing on the market of medical devices and, in particular, of implantable or invasive devices.

The German Medical Association basically welcomes this project because it makes a contribution towards the standardisation and improves the understanding of regulations. The German Medical Association would like to respond to some aspects of the drafts as follows. It should be noted that this statement is divided into two main parts:

- The first part deals with the regulations governing clinical investigations on account of the special significance of this for the ethics committees of the state chambers of physicians;

- the second part contains remarks on additional articles of the draft Regulations.

## *I. Regulations governing clinical investigations*

**General Remarks**

Medical progress and the development of innovative therapies must meet the requirements of protection of test subjects against unreasonable risks and burdens. Since the middle of the 20th century standards have been developed and updated with the objective of application in clinical investigations on medicinal products for human use; these standards have in the meantime gained worldwide recognition. With the 4$^{th}$ amendment to its Medical Devices Act, Germany has utilised this acquired knowledge in the field of medical devices in the interests of the safety, reliability and ethical viability of clinical research on human beings. German legislation governing clinical research with medical devices is therefore based at its core on

the catalogue of ethical principles for medical research involving human subjects documented in the World Medical Association's Declaration of Helsinki.

The proposals of the European Commission outlined here for Regulations of the European Parliament and of the Council on medical devices and in-vitro diagnostic medical devices (hereinafter referred to as: the EU MD Regulation or the EU IVD Regulation) provide for a fundamental new regulation. This regulation is – according to the declared objective – intended on the one hand to eliminate the substantial divergences in interpretation and application of existing regulations, and on the other to create a legal framework which promotes innovative capacity and competitiveness in the medical device industry, and facilitates prompt and reasonably priced access to the market for new products. These objectives are to be approved because they contribute towards swifter public access to innovative therapies. In principle, the harmonisation of legislative standards is to be welcomed as uniform standards create the prerequisites for uniform actions among Member States. However, an equally high level of protection in all Member States can only be achieved if guidelines are formulated in sufficient detail. From the viewpoint of the German Medical Association, the EU MD Regulation lacks this sufficient degree of detail, which is evident from the numerous references to delegated legal documents. Regulatory deficits which could lead to problems in implementation are especially evident in the field of clinical investigations. This is also evident when compared with the scope of the proposed Regulation on clinical trials on medicinal products for human use (COM 2012, 369 final).

Of crucial significance in terms of harmonisation is that the level of protection in terms of the quality and safety of medical devices is improved, and that the safety of test subjects during clinical investigations of medical devices is maintained. The German Medical Association therefore endorses the demand expressed by the European Parliament on 14 June 2012 which, in a resolution prompted by the defective silicon gel breast implants made by the French company PIP (2012/2621(RSP), called upon the European Commission to alter the approval system for certain categories of medical devices – at least for class IIb and class III medical devices – so that approval would be required prior to placing these devices on the market. The measures broached in recitals 40 and 41 for controlling the monitoring of the notified bodies by Member States at EU level according to detailed and strict criteria, as well as strengthening the position of these bodies vis-à-vis manufacturers, especially with regard to unannounced factory inspections, and their right to conduct physical or laboratory tests, are insufficient.

From the perspective of the German Medical Association, a study published in the British Medical Journal (*BMJ* 2012;345:e7090, *How a fake hip showed up failings in European device regulation*) shows that such measures are not sufficient after medical devices have

been brought to the market on account of their differing objectives, but rather that state controls are necessary *prior* to CE marking and the associated certified suitability for marketability within the EU, at least for devices with high risk potential. The freedom of manufacturers to select a notified body anywhere in the EU creates a situation of competitive pricing among a notified bodies, which in turn results in the exploitation of any latitude in regulations in favour of the manufacturers, enabling fast market access for new medical devices to the detriment of device safety. High-risk devices, in particular, demand higher market-access hurdles such as those which exist in the USA for the state licensing of a medical device and an obligatory clinical investigation. The effectiveness and safety of the medical device, and not merely its suitability for the intended purpose, must be documented.In terms of concrete implementation, the draft EU MD Regulation does not satisfy core ethical principles and medical convictions:

1) Among internationally recognised core ethical beliefs in the field of human experimentation is the demand for **justifiability** in terms of benefit and risk. Although Article 50 Par. 3 of the draft EU MD Regulation prescribes that clinical investigations be designed and conducted in a way that the rights, safety and well-being of the subjects participating in a clinical investigation are protected. The risks, which are nevertheless inherent, are not stated in relation to the benefit, at least according to the wording.

2) Internationally recognised standards of protection applying to research involving human subject also state that planned reseach protocols must be submitted to an independent, interdisciplinary **ethics committee** for consideration, comment, guidance and approval before the study begins (Declaration of Helsinki, Rev. 2008, paragraph 15). In compliance with this, the currently applicable Directive 2001/20/EC requires the following for clinical investigations with pharmaceuticals:

The sponsor may not start a clinical trial until the ethics committee has issued a favourable opinion (…) (Article 9, Par. 1, Subpar. 2, Clause 1 of Directive 2001/20/EC).

In the 4th amendment to its medical-device legislation, the German legislative body exercised the option available in European law in accordance with Article 10 Par. 2 Subpar. 2, and Article 10 Par. 2a of Directive 90/385/EEC and Article 15 Par. 2 and Par. 4 of Directive 93/42/EEC, to make the start of the clinical investigation dependent not only on authorisation by the competent authority, but also on the favourable opinion of the ethics committee.

In contrast, the draft for a future Regulation denies Member States the possibility of providing for an independent check by an autonomous ethics committee. According to Annex XIV No.

4.2, as soon as this is available and where applicable according to national law, the opinions drawn up by the "ethics committee(s)" must be submitted later as a supplement to the application for the clinical investigation. **The contribution currently made by the ethics committees to the protection of study participants, to scientific quality and to public confidence in clinical investigations is thereby subverted.** The provisions of Article 51 Par. 6 of the EU MD Regulation concerning the persons assessing the application for the clinical investigation are nowhere near sufficient. They contain neither a fundamental commitment to an independent check by a medical ethics committee, nor do they provide for an equally competent body with the equivalent recognised minimum standards for ethics committees (cf. Article 6 (k) and Article 6 of Directive 2001/20/EC).

a) Although the draft Regulation does not exclude making approval by the competent authority of the respective Member State dependent upon prior scrutiny of the project by an independent ethics committee, the European Commission assumes that it would be sufficient to leave Member States to determine the competent authorities. However, effective protection of the interests of study participants requires that ethics committees be independent, not only of the sponsors and investigators, but also of state agencies – and in particular of agencies which are responsible for the approval of clinical investigations or the licensing of medicines. The peronsal independence of members of ethics committees also prohibits any assignment to a state agency. These aspects must be incoporated in the proposed Regulations.

b) This is even more important in view of the fact that, according to recital 47, the EU MD Regulation should ensure that clinical investigations carried out in the EU are accepted elsewhere. In this respect, the European Commission overlooks the fact that data from clinical investigations for which no favourable opinion by a research ethics committee is available cannot be used in the USA, for example.

c) The German Medical Association is convinced that an adequate evaluation of risks and burdens for study participants, as well as the clinical and scientific benefits of a clinical investigation, can only be carried out by persons who themselves have up-to-date clinical experience and professional expertise. Under the evaluation periods currently proposed, the inclusion of such medical and ethical expertise is rendered impossible.

The German Medical Association objects to the fact that, although the two draft Regulations claim that each individual step of the clinical investigation or clinical performance study complies with recognised ethical principles, as prescribed, *for example,* according to the Declaration of Helsinki (Annex XIV No. 1 of the EU MD Regulation; Annex XII No. 2.2 of the

EU IVD Regulation), this reference is only implied from a material perspective by the European Commission. In a sensitive area of medical activity which is associated with special risks, it is not sufficient that a single researcher continuously measures the project against recognised ethical principles for medical research on human beings. Instead, he or she must be supported in that process by an expert body made up of persons who are familiar with day-to-day clinical routines and can properly assess any questions which arise. The formulation of ethical principles and their analysis by an independent body of ethics experts therefore concern two pillars of the Declaration of Helsinki which, from the perspective of the medical profession, represent an inseparable unit.

3) Medical science serves the further development of diagnostic and therapeutic possibilities and itself strives for new knowledge. In spite of this, one of the core medical convictions governing medical research involving human subjects is that the primary duty is the well-being of the test subject:

In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests. (Declaration of Helsinki, Rev. 2008, Item 6). While the proposal of the European Commission for a draft Regulation on clinical trials on medicinal products for human use (COM 2012, 369) does contain the provision in Article 28 Par. 2 that:

"The rights, safety and well-being of the subjects shall prevail over the interests of science and society."

in contrast, the wording of Article 50 Par. 2 of the EU MD Regulation is significantly weaker and does not prescribe priority:

"Clinical investigations shall be designed and conducted in a way that the rights, safety and well-being of the subjects participating in a clinical investigation are protected (...)"

The German Medical Association deems it necessary for this passage to be supplemented with the requirement that the risks associated with the investigation be medically justifiable in terms of the potential benefits of the medical device. Medical innovation should not be reduced to the supply of new technological developments, but rather must demonstrate (in addition to proof of therapeutic benefit) an acceptable risk-benefit ratio. The draft Regulation is inconsistent insofar as a clinical investigation in accordance with Article 50 Par. 1 (c) of the MD Regulation is carried out, inter alia, for the purpose of evaluating whether undesirable side-effects represent acceptable risks when compared to the benefits expected from the device. In such cases, it would be necessary to be able to refuse approval for the clinical

investigation if the benefit-risk ratio does not justify the involvement of test subjects in the study.

However, this draft Regulation does not do justice to the principle which is laid down in Article 50 Par. 2 of the EU MD Regulation, that clinical investigations be designed and conducted in a way that the rights, safety and well-being of the subjects participating in a clinical investigation are protected.

The German Medical Association shares the conviction which has so far prevailed in Germany, and is historically justified, that persons who cannot give their consent may only be recruited for research projects within very narrow parameters. The same considerations have led to the Federal Republic of Germany not yet signing or ratifying the " Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine" of the Council of Europe in Oviedo (Convention on Human Rights and Biomedicine), which provides for less stringent requirements in this respect.

Recital 49 explains that the coordinated assessment provided for in Article 58 should not include the assessment of intrinsically national, local and ethical aspects of a clinical investigation, including informed consent. Each Member State should retain the ultimate responsibility for deciding whether the clinical investigation may be conducted on its territory. The German Medical Association welcomes this provision if Article 58 Par. 3 (b) means that the other affected Member States take into account the results of the coordinated evaluation. In particular, this means that Member States retain the authority to make decisions on ethical questions – at least as far as the EU Commission is concerned – on their own responsibility for their own territories. The Commission thereby respects the subsidiarity principle and accommodates the fact that there is a divergence of moral ideals and values between Member States, partly for historical reasons.

However, from the perspective of the German Medical Association, the Regulation lacks the necessary clarification that national legislation should be able to render the conduct of clinical investigations involving vulnerable groups dependent upon certain prerequisities, or exclude them altogether (e.g. in the case of convicts).

Against this backdrop, the following text sets out proposed amendments to the draft Regulation which the German Medical Association sees as essential. These include, in particular:

- Effective participation of Member States concerned in the evaluation of the coordinating Member State through

  - an adequate consultation period, before the expiry of which the coordinating Member State may not come to a decision;

  - an obligation on the part of the coordinating Member State to document any remarks and, where appropriate, to justify the reasons for deviating from evidence submitted by a Member State concerned;

- The express involvement of independent ethics committees as defined by the Declaration of Helsinki;

- The guarantee that a negative decision made by an ethics committee would result in denial of approval;

- The inclusion of an explicit opening clause for the introduction of higher standards of protection for vulnerable groups by Member States;

- Monitoring of the conduct of clinical investigations by the competent authorities.

The proposed amendments in this statement are restricted to the EU MD Regulation, but apply correspondingly to the performance-evaluation of in-vitro diagnostic medical devices (e.g. for cerebrospinal fluid sampling), which is regulated in the EU IVD Regulation.

**On the basis of the above, the German Medical Association proposes that the draft Regulation be amended as follows:**

**Amendment 1**

**Article 2 (Definitions)**

| *Commission proposal* | *Amendment proposals* |
|---|---|
| (33) 'clinical investigation' means any systematic investigation in one or more human subjects, undertaken to assess the safety or performance of a device; | (33) (33) 'clinical investigation' means any systematic investigation in one or more human subjects, undertaken to assess the safety***, ~~or~~*** performance ***or effectiveness*** of a device; |
| (37) 'sponsor' means an individual, company, institution or organisation which takes responsibility for the initiation and management of a clinical investigation; | (37) 'sponsor' means an individual, company, institution or organisation which takes responsibility for the initiation***, ~~and~~ management, conduct and/or financing*** of a clinical investigation; |
| | ***(37a (new)) "Inspection" refers to the act by a competent authority of conducting an official review of documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by the competent authority to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organisation's facilities, or at other establishments which the competent authority sees fit to inspect;*** |

*Justification*

***Paragraph 33***

The clinical investigation of a medical device in terms of its effectiveness goes further than the clinical investigation of its performance. It is not only functionality which is investigated, but also the superiority or inferiority in comparison to non-treatment with the medical device. In order to protect the rights and the well-being of participants in such studies, which are frequently conducted independently of the manufacturer, and also those of future patients, in

a fundamentally identical way to the protection afforded participants in clinical investigations conducted in association with manufacturers, an extension of the application area of Articles 50-60 of the Regulation is necessary.

***Paragraph 37***

Including the conduct of the study under the listed responsibilities of the sponsor is necessary on account of the additional obligations of the sponsor contained in Annex XIV Section III of the EU MD Regulation. Otherwise, if the study is customarily deemed to have been concluded following the last visit of the last test subject it would lack reference to the responsibility of the sponsor with regards to associated follow-up tasks, for example the archiving of documentation, the necessary compilation of the clinical investigation report and the publishing of results. Supplementing this paragraph with a reference to the responsibility of the sponsor for financing corresponds to the definition in accordance with Article 2e) of Directive 2001/20/EC.

***Paragraph 37a (new)***

In contrast to the proposal of the Commission for a Regulation on clinical trials on medicinal products for human use (COM 2012, 369 final), the proposed Regulation contains no provisions dealing with inspections. It must not be left to the discretion of the Member States to decide whether to monitor the conduct of clinical investigations. This could lead to decisions on whether to monitor an investigation being made dependent upon the availability of necessary budgetary funds. Furthermore, this could result in clinical investigations being carried out preferentially in states which dispense with monitoring.
A concrete proposal for a new wording in this respect is submitted as Article 59a.

**Amendment 2**

**Article 50 (General requirements regarding clinical investigations)**

| *Proposal by the Commission* | *Amendment Proposals* |
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| (1) Clinical investigations shall be subject to Articles 50-60 and Annex XIV if they are conducted for one or more of the following purposes: | (1) Clinical investigations shall be subject to Articles 50-60 and Annex XIV if they are conducted for one or more of the following purposes: |
| (a) to verify that, under normal conditions of use, devices are designed, manufactured and packaged in such a way that they are suitable for one or more of the specific purposes of a medical device referred to in number (1) of Article 2(1), and achieve the performances intended as specified by the manufacturer; | (a) to verify that, under normal conditions of use, devices are designed, manufactured and packaged in such a way that they are suitable for one or more of the specific purposes of a medical device referred to in number (1) of Article 2(1), and achieve the performances intended as specified by the Manufacturer ***or sponsor***; |
| (b) to verify that devices achieve the | (b) to verify that devices achieve the intended |

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| intended benefits to the patient as specified by the manufacturer; | benefits to the patient as specified by the manufacturer ***or sponsor***; |
| (c) to determine any undesirable side-effects, under normal conditions of use, and assess whether they constitute acceptable risks when weighed against the benefits to be achieved by the device.<br>[....] | (c) to determine any undesirable side-effects, under normal conditions of use, and assess whether they constitute acceptable risks when weighed against the benefits to be achieved by the device.<br>[....] |
| (3) Clinical investigations shall be designed and conducted in a way that the rights, safety and well-being of the subjects participating in a clinical investigation are protected and that the clinical data generated in the clinical investigation are going to be reliable and robust. | (3) Clinical investigations shall be designed and conducted in a way that the rights, safety and well-being of the subjects participating in a clinical investigation are protected and that the clinical data generated in the clinical investigation are going to be reliable and robust. ***They shall not be conducted if the risks associated with the investigation are not medically justifiable in terms of the potential benefits of the medical device.***<br><br>***Member States shall be free to forbid the conduct of clinical investigations involving certain groups of test subjects, or to make such investigations dependent upon specific prerequisites.*** |
| (…) | ***(…)*** |

*Justification*

***Paragraph 1***

*From the perspective of patient protection, it is irrelevant whether a clinical investigation is carried out under the responsibility of a manufacturer and is intended to form the basis for future CE marking, or whether a study is to be conducted for non-commercial, particularly scientific purposes. The German Medical Association therefore demands that clinical investigations which are the responsibility of or are managed by a person or organisation other than a potential manufacturer (cf. Article 2 Par. 37), also be subject to the provisions of the Regulation. The benchmark for the inclusion of clinical investigations in the draft Regulation must be the general principles of Equality before the Law (Article 20 of the EU Charter of Fundamental Rights) and the Right to the integrity of the person (Article 3 of the EU Charter of Fundamental Rights). It must subsequently be determined whether test subjects are put at risk as a result of participation in such an investigation. In contrast, it is not appropriate – as provided for at the present time – to differentiate according to who takes responsiblility for the initiation and management of a clinical investigation.*

*In this connection, we draw attention to the fact that in its proposal for a Regulation*

*governing clinical investigations on medicinal products for human use, the Commission has, with the intended introduction of a national indemnification mechanism set out in Article 73 Par. 3, recognised that even in the case of alleged non-commercial clinical investigations (also known as IITs), subsidies are paid behind the scenes by commercial sponsors. This proposed Regulation is based on the assumption that the objective purpose of a clinical trial should not be to obtain marketing authorisation for a medicinal product. The exclusion of IITs from the scope of application of Articles 50 to 60 and Annex XIV therefore leads to the exclusion of studies with the same risk profile, which in many cases later form the basis for the placing new medical devices on the market after all, even in the context of a clinical evaluation. The differentiation contained within the EU MD Regulation is therefore not factually justified.*

**Paragraph *3***

*The proposed amendment takes into account the fact that medical innovation cannot be reduced to the supply of new technological developments. In addition to proof of therapeutic benefit, it must show an acceptable risk-benefit ratio. The draft Regulation is inconsistent insofar as a clinical investigation in accordance with Article 50 Par. 1 (c) of the MD Regulation, is carried out, inter alia, for the purpose of evaluating whether undesirable side-effects represent an acceptable risk when compared to the benefits expected from the device. In such cases it would be necessary to be able to refuse approval for the clinical investigation if the benefit-risk ratio does not justify the involvement of test subjects in the study.*

*The second amendment is necessary to clarify that national legislation can make the conduct of clinical investigations involving vulnerable groups dependent upon specific prerequisites, or exclude them altogether (e.g. in the case of convicts).*

**Amendment 3**

**Article 51 (*Application for clinical investigations* and favourable opinion by an ethics committee)**

| *Proposal of the Commission* | *Amendment Proposals* |
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| (…) | (…) |
| (2) The sponsor of a clinical investigation shall submit an application to the Member State(s) in which the investigation is to be conducted accompanied by the documentation referred to in Chapter II of Annex XIV. Within six days after receipt of the application, the Member State concerned shall notify the sponsor whether the clinical investigation falls within the scope of this Regulation and whether the application is complete. | (2) The sponsor of a clinical investigation shall submit an application to the Member State(s) in which the investigation is to be conducted accompanied by the documentation referred to in Chapter II of Annex XIV. Within ***~~six~~*** ***14*** days after receipt of the application, the Member State concerned shall notify the sponsor whether the clinical investigation falls within the scope of this Regulation and whether the application is complete. |
| (3) […] | (3) […] |
| Where the Member State has not notified the sponsor according to paragraph 2 within three days following receipt of the comments or of the completed application, the clinical investigation shall be considered as falling within the scope of this Regulation and the application shall be considered complete. | Where the Member State has not notified the sponsor according to paragraph 2 within ***~~three~~*** ***seven*** days following receipt of the comments or of the completed application, the clinical investigation shall be considered as falling within the scope of this Regulation and the application shall be considered complete. |
| (5) The sponsor may start the clinical investigation in the following circumstances: | (5) The sponsor may start the clinical investigation in the following circumstances: |
| (a) in the case of investigational devices classified as class III and implantable or long-term invasive devices classified as class IIa or IIb, as soon as the Member State concerned has notified the sponsor of its approval; | (a) ***~~in the case of investigational devices classified as class III and implantable or long-term invasive devices classified as class IIa or IIb~~***, as soon as the Member State concerned has notified the sponsor of its approval; |
| (b) in the case of investigational devices other than those referred to in point (a) immediately after the date of application provided that the Member State concerned has so decided and that | ***~~(b) in the case of investigational devices other than those referred to in point (a)~~*** ***immediately after the date of application provided that the Member State concerned has so decided and that*** |

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| evidence is provided that the rights, safety and well-being of the subjects to the clinical investigation are protected; | ***~~evidence is provided that the rights, safety and well-being of the subjects to the clinical investigation are protected;~~*** |
| (c) after the expiry of 35 days after the validation date referred to in paragraph 4, unless the Member State concerned has notified the sponsor within that period of its refusal based on considerations of public health, patient safety or public policy. | (***~~c~~b***) after the expiry of ***~~35~~ 60*** days after the validation date referred to in paragraph 4, unless the Member State concerned has notified the sponsor within that period of its refusal based on considerations of public health, patient safety or public policy.<br><br>***Paragraph 5a (new)***<br><br>***Member States shall ensure that a clinical investigation is suspended, cancelled or temporarily interrupted if in the light of new facts it would no longer be approved by the competent authority or if it would no longer receive a favourable opinion from the ethics committee.***<br><br>***Paragraph 6a (new)***<br><br>***Ethics committee***<br><br>***(Subpar. 1) Approval may only be granted if an independent ethics committee has previously submitted a positive evaluation of the clinical investigation. The statement of the ethics committee shall cover in particular the medical justifiability, the consent of the test subject following the provision of full information about the investigation and the suitability of the investigators and investigative facilities.***<br>***(Subpar. 2) The ethics committee serves to protect the rights, safety and well-being of all test subjects, users and third parties. This committee must be independent of the researcher, the sponsor and any other undue influence. It must 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 should be made up of an appropriate number of members, who together are in possession*** |

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| (…) | ***<u>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.</u>***<br><br>***<u>(Subpar. 3) Member States shall take the necessary measures to set up ethics committees and to facilitate their work.</u>***<br><br>*<u>(…)</u>* |

*Justification*

***Paragraph 2***

*The draft Regulation provides for the sponsor being notified within six days as to whether the application is complete and whether the clinical investigation falls within the scope of application of the Regulation. The deadline provided for this does not take into consideration that weekends and public holidays could mean that no time remains for actual examination of the application by the competent authority, and that for this reason the participation of an ethics committee, which for its part may deem certain documentation as essential, is de facto excluded. The German Medical Association therefore demands at least a moderate extension of the deadline.*

***Paragraph 5 (a) and (b)***

*The draft Regulation grants Member States the authority to permit sponsors to commence with the clinical investigation immediately after submission of the application for approval of that clinical investigation, whereby investigations involving investigational devices classified as class III and implantable or long-term invasive devices classified as class IIa or IIb, are excepted. In addition, evidence is required that that the rights, safety and well-being of the subjects to the clinical investigation are protected.*

*This opt-out provision leads to pressure on Member States to permit the commencement of clinical investigations – according to the current draft Regulation – 35 days earlier than in other Member States, and therefore to relegate the protection of test subjects in favour of competitive advantages. At the same time, it must be taken into consideration that clinical investigations in this sector are only carried out if a clinical evaluation is not sufficient anyway, i.e. when there are uncertainties regarding the functional suitability, side-effects or risks associated with the use of a medical device. If only clinical investigations related to the suitability, performance, benefits, side-effects and an acceptable benefit-risk analysis are subject to the EU MD Regulation, in accordance with Article 50, Paragraph 1, the protection of test subjects dictates that they be protected in every Member State by an approval process conducted by the competent authority and an evaluation process conducted by the ethics committee in order to safeguard them from useless, inappropriate and risky medical devices. In addition, this means that it is accepted that those test subjects who are the first to*

*be subjected to the clinical investigation enjoy less protection than those who participate at a later date. While the first test subjects participate on the basis of the representations of the sponsor, the latter enjoy the benefit of the knowledge made available by the competent authority and / or ethics committee.*

***Paragraph 5 (c)***

*The adjustment of the deadline is necessary in order to facilitate an effective assessment of the clinical investigation. Particularly, in the case of clinical investigations conducted in several Member States, sufficient time must remain for coordinated evaluation in accordance with Article 58. As the draft Regulation does not provide for any special evaluation deadline for multinational clinical investigations, the general evaluation deadline in this Regulation must be appropriately adjusted.*

*The draft Regulation does not prescribe any circumstances on the basis of which approval is to be denied. For the protection of test subjects, the prerequisites specified in the list, must under all circumstances, result in a denial of approval.*

***Paragraph 5a (new)***

*Article 56 provides for an exchange of information between Member States insofar as one Member State orders the suspension, cancellation or temporary interruption of a clinical investigation. However, the EU MD Regulation does not regulate the circumstances under which a Member State is entitled to make such a decision. This can only be the case if new information is available which would stand in the way of an approval.*

***Paragraph 6a (new) Subparagraphs 1 and 2***

*Clinical investigations are designed and carried out in accordance with Article 50 Par. 3 in such a manner that the protection of the rights, safety and well-being of the subjects participating in a clinical investigation are protected. To implement those objectives, it is necessary to make approval by Member States dependent upon the decision of the competent, independent, interdisciplinary ethics committee formed under their respective national laws. A negative decision handed down by an ethics committee must necessarily result in the denial of approval for a clinical investigation. At the same time, the ethics committee must be independent of the sponsor and the investigators, as well as of state agencies – in particular those state agencies responsible for the approval of a clinical investigation or the licensing of medicines. The proposed Paragraph 6a complies with that requirement and secures the level of protection for test subjects, and is in harmony with internationally recognised protection standards, as set out in the Declaration of Helsinki.*

***Paragraph 6a (new) Subparagraph 3***

*With the express regulation of ethics committees, an EU Regulation can make a substantial contribution towards setting up independent ethics committees in accordance with international ethical standards for the protection of the rights, safety and well-being of study participants, including in countries in which this has not been the case until now. Dispensing with the requirement of independent ethics committees will weaken this independent protection of study participants in third countries, and also in numerous Member States. This stands in contradiction to the objective declared in recital 47, that clinical investigations conducted outside the Union in accordance with international guidelines can be accepted under this Regulation.*

**Amendment 4**

**Article 54 (Clinical investigations with devices authorised to bear the CE marking)**

| *Proposal of the Commission* | *Amendment Proposals* |
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| (1) Where a clinical investigation is to be conducted to further assess a device which is authorised in accordance with Article 42 to bear the CE marking and within its intended purpose referred to in the relevant conformity assessment procedure, hereinafter referred to as 'post-market clinical follow-up investigation', the sponsor shall notify the Member States concerned at least 30 days prior to their commencement if the investigation would submit subjects to additionally invasive or burdensome procedures. Article 50(1) to (3), Article 52, Article 55, Article 56(1), Article 57(1), the first subparagraph of Article 57(2) and the relevant provisions of Annex XIV shall apply. | (1) Where a clinical investigation is to be conducted to further assess a device which is authorised in accordance with Article 42 to bear the CE marking and within its intended purpose referred to in the relevant conformity assessment procedure, hereinafter referred to as 'post-market clinical follow-up investigation', the sponsor shall notify the Member States concerned at least 30 days prior to their commencement if the investigation would submit subjects to additionally invasive or burdensome procedures. Article 50(1) to (3), ***Article 51***, Article 52, Article 55, Article 56(1), Article 57(1), the first subparagraph of Article 57(2), ***Article 58*** and the relevant provisions of Annex XIV shall apply. |

*Justification:*

*The EU MD Regulation provides that competent authorities be notified of clinical investigations with CE-marked medical devices during which test subjects are subjected to additional invasive or burdensome processes during the investigation 30 days prior to commencement, and that an approval process and evaluation by the ethics committee be carried out only in cases where the device is to be used for a purpose other than that specified by the manufacturer and stated in the relevant conformity-evaluation. The differentiation is not objectively justified and is also not linked to the danger of the invasive or burdensome process, but excludes clinical investigations with such dangerous invasive or burdensome processes as cerebrospinal fluid sampling from the obligation to obtain prior approval.*

*In addition, it remains unclear as to why notification of the clinical investigation must be given 30 days in advance. The apparent thinking behind this is that the approving authority should have the authority to suspend the investigation. However, this is apparent only indirectly from the reference to Article 56, according to which the other members states are to be informed about such a suspension. As a result, it remains unclear as to which standard is to be applied to such a suspension order. Furthermore, because no reference is made to Annex XIV, the competent authority cannot access documentation in order to assess the danger posed by the clinical investigation.*

**Amendment Proposal 5**

**Article 59a (new) (Supervision by Member States)**

| *Proposal of the Commission* | *Amendment Proposals* |
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| | ***1. Member States shall appoint inspectors to supervise compliance with this Regulation. They shall ensure that those inspectors are adequately qualified and trained.***<br><br>***2. Inspections shall be conducted under the responsibility of the Member State where the inspection takes place.***<br><br>***3. Where a Member State concerned intends to carry out an inspection with regard to one or several clinical trials which are conducted in more than one Member State concerned, it shall notify its intention to the other Member States concerned, the Commission and the Agency, through the EU portal, and shall inform them of its findings after the inspection.***<br><br>***4. The Agency shall coordinate cooperation on inspections between Member States and on inspections conducted by Member States in third countries.***<br>***5. Following an inspection, the Member State under whose responsibility the inspection has been conducted shall draw up an inspection report. That Member State shall make the inspection report available to the sponsor of the relevant clinical trial and shall submit the inspection report through the EU portal to the EU database. When making the inspection report available to the sponsor, the Member State referred to in the first subparagraph shall ensure that confidentiality is protected.***<br><br>***6. The Commission shall specify the*** |

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| | ***modalities for the inspection procedures by the way of implementing acts. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 84(2).*** |

*Justification*

In contrast to the proposal of the Commission for a Regulation on clinical trials on medicinal products for human use (COM 2012, 369 final), the proposed Regulation contains no provisions regarding inspections. It must not be left to the discretion of the Member States to decide whether to monitor the conduct of clinical investigations. This could lead to decisions on whether to monitor an investigation being made dependent upon the availability of appropriate budgetary means. This could result in clinical investigations being carried out preferentially in states which dispense with monitoring. The concrete wording of the proposal follows Articles 75 and 76 of the proposal of the Commission for a Regulation on clinical trials on medicinal products for human use (COM 2012, 369 final).

**Amendment 6**

**Annex XIV – Clinical Investigations**

| *Proposal of the Commission* | *Amendment Proposals* |
|---|---|
| 1. Ethical considerations<br>Every step in the clinical investigation, from first consideration of the need and justification of the study to the publication of the results, shall be carried out in accordance with recognised ethical principles, as for example those laid down in the<br>World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the 18th World Medical Association General Assembly in Helsinki, Finland, in 1964, and last amended by the 59th World Medical Association General Assembly in Seoul, Korea, in 2008. | 1. Ethical considerations<br>Every step in the clinical investigation, from first consideration of the need and justification of the study to the publication of the results, shall be carried out in accordance with recognised ethical principles, as for example those laid down in the<br>World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the 18th World Medical Association General Assembly in Helsinki, Finland, in 1964, and last amended by the 59th World Medical Association General Assembly in Seoul, Korea, in 2008.<br>***The regulation of more detailed prerequisites regarding the involvement of test subjects in clinical investigations shall be the responsibility of the Member States.*** |

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| (…) | *(…)* |
| 3.1.3. Information on the principal investigator, coordinating investigator, including their qualifications, and on the investigation site(s). | 3.1.3. Information on the principal investigator, coordinating investigator, including their qualifications, and on the investigation site(s) ***as well as details of the contracts concluded between the sponsor and the investigating agency / investigator, including details of remuneration and financing.*** |
| 3.1.4. Overall synopsis of the clinical investigation. | 3.1.4. Overall synopsis of the clinical investigation ***in the national language of each of the affected Member States.*** <br><br> ***3.15.a (new) A plan for the further treatment and medical care of test subjects following conclusion of the clinical investigation.*** |
| (…) | *(…)* |

*Justification*

***Regarding 1.***
*This ammendment serves to clarify that the Member States must define the prerequisites for the participation of test subjects in clinical investigations. In this respect they are bound to the definitions of minimum standards set out in the Declaration of Helsinki of the World Medical Association in the version of 2008.*

***Regarding 3.1.3.***
*It is standard practice for ethics committee to be given access to the contracts concluded between the sponsor and the investigating agency/investigator and to take these into consideration in the evaluation of the study protcoll.*

***Regarding 3.1.4.***
*In order to facilitate an objective evaluation of the application, a synopsis of the investigative plan in the respective national language is of central significance.*

***Regarding 3.15.a (new)***
*The Declaration of Helsinki provides that the protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.*

## *II. Remarks on other Articles of the draft Regulation*

a) Proposed Regulation on medical devices [COM (2012) 542]

**Article 2: Definitions**

With regard to definition no. (1) "Medical device" pertaining to “devices and software”, a differentiation should be made between these, as opposed to “hardware and software which are used exclusively for administrative purposes in healthcare”. In this area there are repeatedly attempts to escalate costs by designating hardware and software in toto as medical devices as soon as they are used in healthcare contexts. In view of the prevailing pressure on costs, this cannot be justified. The German Medical Association asks for clarification that these do not refer to medical devices within the meaning of this Regulation. The same applies to No. (4) "active medical device", last sentence.

**Article 15: " *Single-use devices and their reprocessing*"**

The attempt to integrate an Article in the Regulation which provides a solution to the discussion which has taken place in the past on many different levels, and not always free of vested interests, in respect to the possibilities and limitations of reprocessing disposable devices, appears to have failed. The fundamental problem associated with a proper differentiation between the reprocessing of formally approved devices and devices which according to the manufacturer are not suitable for reprocessing is not tackled at all. Rather, the Commission itself should be able to define categories or groups of disposable devices which may be re-used after reprocessing. To what extent this is permissible at all is questionable. After all, the properties of the devices as defined by their manufacturers would be re-defined by this.
Furthermore, as a result of the wording of Article 15 of the draft Regulation, it cannot be ruled out that healthcare facilities which carry out reprocessing of disposable devices at their own risk act in such situations as manufacturers, with all of the associated consequences. This represents a case of over-regulation. Instead of this new regulation, it would make more sense to persuade EU Member States to bring the reprocessing of medical devices as a whole – regardless of whether they are formally declared as suitable for reprocessing or as disposable – up to the most modern scientific and technological standards through training and qualified monitoring. Apart from this, the impression is created that this regulation opens a back door to the imposition of a ban on the reprocessing of devices which have been

declared by their manufacturers as disposable. This would certainly be of benefit to the manufacturer, however not necessarily to the user, let alone the patient.

Proposal of the German Medical Association: Delete Article 15

**Ammendment 7**

**Article 15 (Single-use devices and their reprocessing)**

| *Proposal of the Commission* | *Amendment Proposals* |
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| (1) Any natural or legal person who reprocesses a single-use device to make it suitable for further use (…). | ~~(1) Any natural or legal person who reprocesses a single-use device to make it suitable for further use (…).~~ |
| (2) Only single-use devices that have been placed on the Union market in accordance with this Regulation, or (…). | ~~(2) Only single-use devices that have been placed on the Union market in accordance with this Regulation, or (…).~~ |
| (3) In the case of reprocessing of single-use devices for critical use (…). | ~~(3) In the case of reprocessing of single-use devices for critical use (…).~~ |
| (4) The Commission, by means of implementing acts, shall establish and regularly update a list of categories or (…). | ~~(4) The Commission, by means of implementing acts, shall establish and regularly update a list of categories or (…).~~ |
| (5) The name and address of the legal or natural person referred to in paragraph 1 and the other relevant (…). | ~~(5) The name and address of the legal or natural person referred to in paragraph 1 and the other relevant (…).~~ |
| (6) A Member State may maintain or introduce national provisions prohibiting (…). | ~~(6) A Member State may maintain or introduce national provisions prohibiting (…).~~ |

b) Proposed Regulation on *in vitro* diagnostic medical devices [COM (2012) 541]

**Article 4, Paragraph 5**

In contrast to the situation for the commercial manufacturing of *in vitro* diagnostic medical devices, facilities which manufacture devices as defined in Annex 7, Classes A, B and C for use in their own facilities must adhere to a specific system of quality management. This restriction on freedom of action does not make sense. It is also particularly critical to the extent that it affects not only the laboratory in which *in vitro* diagnostic devices may be

manufactured for own use, but also the whole hospital. The naming of a specific QM standard is to be rejected. Although this is moderated by reference to the fact that another, equivalent standard could also be applied, experience shows that the naming of concrete standards tends to develop a life of its own, especially in the context of the monitoring of compliance with legal regulations governing medical devices. For this reason, there is an urgent necessity for facilities which manufacture *in vitro* diagnostic devices for their own use also to be granted the same freedom of action as that enjoyed by laboratories which are involved in the commercial manufacture of *in vitro* diagnostic devices.
It should also be noted that DIN EN ISO 15189 was specifically designed for laboratories which are engaged in routine care. The special aspects which may possibly be taken into consideration in the manufacture of *in vitro* diagnostic devices are not represented in this standard in any way.

## Ammendment 8

**Article 4 (*Placing on the market and putting into service*)**

| *Proposal of the Commission* | *Amendment Proposals* |
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| […] | […] |
| (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. | (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~~ that the health institution~~'s single~~ **has an appropriate quality management system in place according to Article 8 Par. 5 of this Regulation**~~, 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 | 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 |

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| devices concerned subject to further safety requirements.<br><br>Devices classified as class D in accordance with the rules set out in Annex VII, even if manufactured and used 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.<br><br>[…] | devices concerned subject to further safety requirements.<br><br>Devices classified as class D in accordance with the rules set out in Annex VII, even if manufactured and used 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.<br><br>[…] |

**Annex I, No. 16**

This puts devices which are intended by the manufacturer for self-testing and devices which require professional application in the same category. This is not appropriate because it makes no differentiation between members of the health professions and non-medical persons. This poses a threat to patient safety.

The German Medical Association proposes the deletion of the words "or near-patient testing" where they appear, and justifies this with the fact that only specialist personnel who have been appropriately trained and instructed may conduct these test procedures.

## Ammendment 9

**Annex I (General Safety and Performance Requirements)**

| *Proposal of the Commission* | *Amendment Proposals* |
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| […]<br><br>(16) **Protection against the risks posed by devices intended by the manufacturer for self-testing or near-patient testing**<br><br>16.1. The devices intended for self-testing or near-patient testing shall be designed and manufactured in such a way that they perform appropriately for their intended | […]<br><br>(16) **Protection against the risks posed by devices intended by the manufacturer for self-testing ~~or near-patient testing~~**<br><br>16.1. The devices intended for self-testing ~~or near-patient testing~~ shall be designed and manufactured in such a way that they perform appropriately for their intended |

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| purpose taking into account the skills and the means available to the intended user and the influence resulting from variation that can be reasonably anticipated in the intended user's technique and environment. The information and instructions provided by the manufacturer shall be easy for the intended user to understand and apply. | purpose taking into account the skills and the means available to the intended user and the influence resulting from variation that can be reasonably anticipated in the intended user's technique and environment. The information and instructions provided by the manufacturer shall be easy for the intended user to understand and apply. |
| 16.2. The devices intended for self-testing or near-patient testing shall be designed and manufactured in such a way as to | 16.2. The devices intended for self-testing ~~or near-patient testing~~ shall be designed and manufactured in such a way as to |
| – ensure that the device is easy to use by the intended user at all stages of the procedure; and **EN** 92 **EN** | – ensure that the device is easy to use by the intended user at all stages of the procedure; and **EN** 92 **EN** |
| – reduce as far as possible the risk of error by the intended user in the handling of the device and, if applicable, the specimen, and also in the interpretation of the results. | – reduce as far as possible the risk of error by the intended user in the handling of the device and, if applicable, the specimen, and also in the interpretation of the results. |
| 16.3. The devices intended for self-testing and near-patient testing shall, where reasonably possible, include a procedure by which the intended user can: | 16.3. The devices intended for self-testing ~~and near-patient testing~~ shall, where reasonably possible, include a procedure by which the intended user can: |
| – verify that, at the time of use, the device will perform as intended by the manufacturer; and | – verify that, at the time of use, the device will perform as intended by the manufacturer; and |
| – be warned if the device has failed to provide a valid result. | – be warned if the device has failed to provide a valid result. |
| […] | […] |