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PART II - Annex 1

COMMISSION STAFF WORKING DOCUMENT

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

Accompanying the documents

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

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

and

on in vitro diagnostic medical devices

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Table of contents

1. PROBLEM DEFINITION

1.1. Problem MD-1: Scope - regulatory gaps or uncertainties

1.1.1. Products manufactured utilising non-viable cells or tissues of human origin

At the occasion of the adoption of the IVDD, the legislator in recital (35) called for the adoption of legislation on medical devices manufactured using substances of human origin[1]. So far, this mandate has only been partly fulfilled. Firstly, Directives 2000/70/EC and 2001/104/EC subjected medical devices incorporating a medicinal substance derived from human blood or plasma to the AIMDD and the MDD. Secondly, Regulation (EC) No 1394/2007 concerning advanced therapy medicinal products (ATMP Regulation)[2] covers medical devices which are combined with *viable* human or animal cells or tissues or with *non-viable* human or animal cells or tissues which are liable to act upon the human body with action that can be considered as primary to that of the medical device. Directive 2004/23/EC concerning human tissues and cells[3] appears to cover appropriately non-viable human tissues and cells that are not substantially manipulated[4] and products derived from such tissues and cells. It applies to the "donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells intended for human applications and of manufactured products derived from human tissues and cells intended for human applications" unless such manufactured products are covered by other directives. Recital (6) of Directive 2004/23/EC states that tissues and cells to be used for industrially manufactured products, including medical devices, should be covered by that directive only as far as donation, procurement and testing of the tissues and cells are concerned.

Except for medical devices incorporating a medicinal substance derived from human blood or plasma, devices incorporating or derived from human tissues or cells are currently exempted from the AIMDD and MDD[5]. This means that certain products which are manufactured utilising *non-viable* human[6] cells or tissues, other than those that have undergone only non-substantial modification, and which do not act principally by metabolic, immunological or pharmacological means fall into a regulatory gap at Union level as far as Directive 2004/23/EC is not applicable. They are regulated under different systems in the Member States or are not specifically regulated at all which has been identified by manufacturers as a

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1 IVD manufactured from tissues, cells or substances of human origin are covered by the IVDD, see its recital (32).

2 Article 2(1)(d) of Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004.

3 Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cell, OJ L 102 of 7.4.2004, p.48.

4 Annex I of Regulation (EC) No 1394/2007 contains a non-exhaustive list of manipulation considered non-substantial.

5 See Article 1(6)(c) of Directive 90/385/EEC and Article 1(5)(f) of Directive 93/42/EEC

6 Medical devices which are manufactured utilising *non-viable* animal tissues which do not act principally by metabolic, immunological or pharmacological action, however, are covered by the medical device directives and specific requirements apply, e.g. Commission Directive 2003/32/EC introducing detailed specifications as regards the requirements laid down in Directive 93/42/EEC with respect to medical devices manufactured utilising tissues of animal origin.

significant obstacle for the development of tissue-engineered devices in Europe[7]. The Council, in its Conclusions on innovation in the medical device sector, invited the Commission to consider "*how to address the regulatory gaps in the system, for instance in relation to medical devices manufactured utilising non-viable human cells and tissues*"[8].

When Directive 2007/47/EC was adopted, the Commission committed to consider proposals for the appropriate regulation to cover any regulatory gap which might remain at EU level after the adoption of the ATMP Regulation.

1.1.2. Implantable or other invasive products without a medical purpose

It is currently not clear whether implantable or other invasive products for which the manufacturer does not claim a medical purpose, but e.g. an aesthetic or cosmetic purpose, are covered by the AIMDD or MDD or not. Some argue that the third indent of the 'medical device' definition in Article 1(2)(a) of the MDD covers any device which pursues the purpose of "investigation, replacement or modification of the anatomy or of a physiological process", regardless of whether the manufacturer attributes to it a medical or a non-medical (e.g. aesthetic) purpose. However, according to the prevailing interpretation of the Commission, Member States and stakeholders, a device falls within the definition of a medical device when it pursues a medical purpose[9]. The question is currently pending before the European Court of Justice for a preliminary ruling[10].

Typical invasive "aesthetic products" (e.g. non-corrective contact lenses; wrinkle fillers; implants for augmentation of specific body parts such as breast, lips, gluteus, calf, pectoral etc.) belong to the same type of products than those with a medical purpose, have similar risk features than their related medical devices and are often used in a medical environment (aesthetic or plastic surgery). The use of implantable or other invasive products for aesthetic or other non-medical purposes is constantly growing and concerns were voiced by Members of the European Parliament[11], competent authorities and stakeholders[12] regarding the regulatory control of such products.

Assuming that products without a medical purpose are not covered by the MDD, Directive 2001/95/EC on general product safety (GPSD)[13] is applicable to the extent that the products are intended or likely to be used by consumers. The GPSD, however, only sets general requirements and does not make provision for a pre-market assessment.

Assuming that products which pursue the purpose of investigation, replacement or modification of the anatomy or of a physiological process are covered by the MDD, even without a medical purpose, there would still remain a considerable grey area as regards for

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7 See minutes of the MHRA Medical Device Technology Forum on tissue engineering, held on 27.11.2008, http://www.mhra.gov.uk/home/groups/clin/documents/websiteresources/con035987.pdf

8 Council Conclusions adopted on 6 June 2011, section 6, 13th indent.

9 MEDDEV 2.1/1 of April 1994: Definition of medical devices, accessory and manufacturer, http://ec.europa.eu/health/medical-devices/files/meddev/2_1-1___04-1994_en.pdf.

10 The German Federal Supreme Court (Bundesgerichtshof) has submitted this question to the ECJ for a preliminary ruling (BGH I ZR 53/09, Decision of 7 April 2011; ECJ C-219/11).

11 See written questions E-3878/10, E-1878/10, E-4071/09.

12 Clinica, August 2010 p. 26, "Aesthetic device scandal threatens to bring whole industry down with it"; Clinica, Sept/Oct. 2010, p. 12, "Aesthetic devices: Is specific EU legislation needed?"

13 Directive of the European Parliament and of the Council of 3 December 2001 on general product safety, OJ L 11 of 15.1.2002, p.4.

example non-corrective contact lenses because they would most likely not be considered as modifying the anatomy or a physiological process.

1.1.3. Reprocessing of single-use medical devices

The reprocessing of a medical device includes steps needed to allow its safe reuse such as routine maintenance, disassembly, cleaning, disinfection and/or sterilization. It is a common practice for reusable devices (e.g. surgical instruments) but it is also carried out regarding devices for single use (e.g. angioplasty catheters). Only the latter practice is subject to discussion in this impact assessment.

The concept of single use device (SUD)[14] was introduced in the MDD by Directive 2007/47/EC. The regulation is currently limited to information requirements on the label and in the instructions for use[15]. Few Member States (e.g. Germany) allow the reprocessing of SUD and have developed guidelines[16], other Member States prohibit (e.g. France) or discourage (e.g. UK) SUD reprocessing whilst most Member States do not have specific regulations on this issue. At international level, the regulatory approaches differ as well. Whilst in Japan the reprocessing of SUD is prohibited, around 10 third party reprocessors are established in the US where the reprocessing of some SUD is performed and where, according to FDA regulations, reprocessors of SUD are considered as manufacturers[17].

The reprocessing is either done 'in house' by the users (e.g. hospitals) or by an external reprocessing company. According to information provided by the reprocessing industry, 50-60 external reprocessing companies are established in Europe, but only four of them (all established in Germany) carry out reprocessing of SUD. Even for the European market leader, it appears to remain a limited part of their business.

Article 12a of the MDD, introduced by Directive 2007/47/EC, required the Commission to submit a report to the European Parliament and to the Council on the issue of reprocessing of medical devices and to submit any proposal it would deem appropriate in the light of the findings of this report in order to ensure a high level of health protection in relation to this practice. Based on a Scientific Opinion of the SCENIHR[18], the Commission submitted the report in August 2010[19] in which it described the public health aspects as well as ethical, environmental and economic aspects in relation to reprocessing of SUD. In terms of public health and patient safety, the risks are especially related to remaining pathogenic micro-organisms, persistence of chemical substances used during reprocessing and alteration of performance of the device.

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14 According to Article 1(2)(n) of Directive 93/42/EEC 'single use device' means "a device intended to be used once only for a single patient".

15 Annex I, sections 13.3(f) and 13.6(h) MDD. There it is also required that the manufacturer's indication of single use must be consistent across the EU.

16 Empfehlung der Kommission für Krankenhaushygiene und Infektionsprävention beim Robert-Koch-Institut und des Bundesinstituts für Arzneimittel und Medizinprodukte, "Anforderungen an die Hygiene bei der Aufbereitung von Medizinprodukten", 1.11.2001, http://www.rki.de/cln_116/nn_201414/DE/Content/Infekt/Krankenhaushygiene/Kommission/Downloads/Medpro__Rili,templateId=raw,property=publicationFile.pdf/Medpro_Rili.pdf

17 See Report of the United States Government Accountability Office (GOA), Reprocessed single-use medical devices, Jan. 2008, http://www.gao.gov/new.items/d08147.pdf.

18 SCENIHR, 15.4.2010, The Safety of Reprocessed Medical Devices Marketed for Single Use.

19 Report of 27 August 2010 on the issue of the reprocessing of medical devices in the European Union, in accordance with Article 12a of Directive 93/42/EEC, COM(2010)433 final.

1.2. Problem MD-2: Adaptation of legal requirements to technological, scientific and regulatory developments

All in all, the MDD appropriately captures new technologies. In particular, the essential requirements and the classification rules usually are sufficiently flexible to apply also to innovative devices. Several amendments were introduced in the essential requirements and classification rules by Directive 2007/47/EC which became applicable in March 2010. Some aspects, however, which are related to the appropriate risk-assessment regarding devices using material or technologies with a potentially increased risk were not yet sufficiently mature at the moment of this latest revision or have come to light subsequently due to post-market experience.

Examples: Medical devices with nanomaterial; ingested devices; assisted reproductive technologies; agents for organ conservation; apheresis systems; products incorporating living microorganisms.

In the absence of specific classification rules and essential requirements, the existing provisions are interpreted and implemented in different ways by the Member States leading to different levels of protection of public health and patient safety as well as to obstacles to the free movement of products.

Nanomaterial is used in medical devices still to a limited extent but their use is expected to grow. Examples for nanotechnology in medical devices are cancer therapy, joint or mesh implants, blood vessel prosthesis[20]. In some cases (e.g. cancer therapy) the nanomaterial is intended to be released in the body. The Commission's working group on New and Emerging Technologies in Medical Devices (N&ET) in July 2007 presented a report on nanotechnology and suggested, among others, a specific classification rule (class III) for medical devices which incorporate or consist of "free" nanomaterial. With a view to the potential increase of nanotechnology used in devices and the regulatory development in this field (e.g. Commission Recommendation 2011/696/EU on the definition of nanomaterial), appropriate regulation should be considered for this revision of the MDD.

1.3. Problem MD-3: Clinical evaluation and clinical investigations, in particular those carried out in more than one Member State

As part of the essential requirements to be fulfilled according to the AIMDD and MDD, a medical device must not – subject to a risk/benefit analysis – compromise the safety of patients, users or other persons and it must achieve the (clinical) performance intended by the manufacturer. The manufacturer must demonstrate the conformity with the essential requirements on the basis of clinical data (clinical evaluation) which is laid down in Annex VII of the AIMDD and Annex X of the MDD. A clinical evaluation may be based either on relevant scientific literature or on results of a clinical investigation (or on both). The concept of 'performance'/'clinical performance', however, is not very clear and has prompted concerns that demonstration of the clinical benefit was not sufficiently required when demonstrating the intended performance.

The EU regulation of clinical investigations regarding medical devices is not very extensive and consists only of Article 10, Annex 6 sections 2.2 and 3.2, and Annex 7, section 2 of the AIMDD and Article 15, Annex VIII sections 2.2 and 3.2, and Annex X, section 2 of the

[20] See AFSSAPS, Evaluation biologique des dispositifs médicaux contenant des nanomatériaux, 22.2.2011; BVMed, Nanotechnologien in der Medizintechnik, 27.4.2011; 4th European Conference for Clinical Nanomedicine (CLINAM 2011), www.clinam.org.

MDD. These provisions require manufacturers or authorised representatives to notify the competent authorities where the investigation shall be conducted 60 days before its start, to draw up a statement and documentation regarding procedural and safety requirements and to conduct the investigation in conformity with ethical considerations and according to a predefined methodology.

The absence of a full-fledged regulation of clinical investigations is not considered a problem and the issue of clinical investigation has not been mentioned in the questionnaire of the 2008 public consultation. But some responses to the public consultation raised concerns regarding the lack of harmonisation between national competent authorities regarding the approval of investigations. The Commission's Clinical Investigation and Evaluation (CIE) Working Group listed issues where legislative clarifications (e.g. introduction of the notion "sponsor") and a better coordination amongst Member States would improve the EU regulations in this field. Also the High Level Group on Administrative Burden suggested the introduction of a single approval procedure for clinical investigations in the field of medical devices carried out in more than one Member State[21].

The assessment of notifications of clinical investigations falls in the responsibility of every individual Member State. The competent authority assesses the technical and safety aspects whilst ethical aspects are assessed by ethics committees. Currently, the medical devices directives only make provision for an exchange of information between Member States when a clinical investigation is refused, halted, significantly modified or temporarily interrupted (Article 10(3) AIMDD and Article 15(6) MDD), but they do not require any coordination of the assessment by the competent authorities involved when a clinical investigation is conducted in more than one Member State.

According to surveys conducted in the framework of the CIE working group, an increase can be noted as regards pre-market clinical investigations notified to EU/EFTA national authorities. This increase may be linked to the reinforcement of the requirements regarding clinical evaluation and clinical investigations by Directive 2007/47/EC which came into application in 2010:

Year	2008	2009	2010
Notifications of pre-market clinical investigations	ca. 529	ca. 660	ca. 719

These figures give an indication but are not exact since some national competent authorities did not provide data while other authorities counted pre-market clinical investigations and performance evaluations for IVD together. Data for 2008 suggest that roughly 30% of clinical investigations are conducted in more than one Member State. For 2009 and 2010, half of the national competent authorities have not provided data distinguishing between national and multi-national investigations. But according to those who did, the number of national and

[21] Opinion of 20 January 2009 (recommendation 18), http://ec.europa.eu/enterprise/policies/better-regulation/files/090114_finver_hlg_en.pdf.

multi-national investigations is almost half/half[22]. It can be estimated that between 200 and 350 clinical investigations a year are conducted in more than one Member States. In terms of patients enrolled in multi-national investigations, it can be estimated that their number is higher than the number of patients enrolled in pure national investigations[23].

The overall approval (or non-objection) rate is high, either on initial assessment or after submission of supplementary information (the practice differs considerably between Member States). Data available for 2008 suggest that the rate of multi-national investigations which are approved only after supplementary information is relatively high (67%) compared to single country investigations which in their majority are approved on initial assessment. These figures suggest that multi-national clinical investigations tend to give rise to more queries for additional information than pure national investigations which need to be dealt with by the applicant.

The fact that manufacturers/sponsors must submit their documentation to each competent authority and are then subject to multiple queries for additional information increases their administrative costs. In addition, the assessments of the competent authorities concerned may lead to different outcomes as regards technical and safety aspects related to the same device intended for clinical investigation. This also means that patients participating in the same multi-national investigation are subject to different safety levels. Moreover, the revision of the AIMDD/MDD provides the opportunity to align the provisions regarding clinical investigations on medical devices, where appropriate, with the recently adopted Proposal for a Regulation on clinical trials on medicinal products for human use[24].

2. OBJECTIVES

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

- **Objective MD-1: Covering of legal gaps and loopholes**
- **Objective MD-2: Appropriate legal requirements taking into account technological, scientific and regulatory developments**
- **Objective MD-3: Enhanced legal certainty and coordination in the field of clinical evaluation and investigations, in particular those conducted in more than one Member State**

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22 For 2009: 98 national CI and 104 multi-national CI; for 2010: 138 national CI and 127 multi-national CI. However, the two Member States with the highest number of CI notifications (DE, FR) did not distinguish between national and multi-national CI.

23 For medicinal products, between 4,000 and 6,000 clinical trials are performed each year in the EU/EFTA. Even though it is not possible to extrapolate from data available for clinical trials for pharmaceuticals, the fact that around 25% of clinical trials for pharmaceuticals involve more than one EU/EFTA country which account for around 70% of trial subjects suggests that multi-national clinical investigations for medical devices are also larger and account for more patients subject to the investigations.

24 COM(2012)369.

3. POLICY OPTIONS

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

3.1.1. Products manufactured utilising non-viable human cells and tissues

To cover the regulatory gap regarding products manufactured utilising non-viable human cells and tissues, other than those that have undergone only non-substantial manipulation, basically two options need to be assessed: to regulate these products as medicinal products or as medical devices. The "no EU action" needs to be discarded since it would not change anything to the current unsatisfactory situation.

3.1.1.1. Policy option MD-1A: Regulate products manufactured utilising non-viable human cells and tissues as medicinal products

This option would subject products which are manufactured utilising non-viable human cells and tissues to the medicinal products legislation and would thus require the extension of the scope of Regulation (EC) No 1394/2007 concerning advanced therapy medicinal products.

3.1.1.2. Policy option MD-1B: Regulate products manufactured utilising non-viable human cells and tissues as medical devices

This option would subject products which are manufactured utilising non-viable human cells and tissues (and which are not covered by the ATMP Regulation) to the legislation on medical devices. It would require the adoption of specific requirements regarding the safety of the products (especially regarding the risk of transmissible infectious agents) and their traceability. In addition, a consultation procedure allowing competent authorities to verify the safety of the processed human tissues/cells could be envisaged, as well as a consultation EMA Committee of Advanced Therapies (CAT) in order to ensure consistency as regards the possible borderline cases between ATMP and medical devices which could arise due to questions concerning the principal mode of action of the product manufactured utilising human tissues or cells or the status as viable or non-viable of these tissues or cells.

3.1.2. Implantable or other invasive products without a medical purpose

For products with aesthetic or other non-medical purposes, the pivotal question is whether to regulate them within the medical devices legislation or not. Two options are to be considered: one would lead to the application of the medical devices legislation and the other option would require the adoption of a separate legislation. The option to apply the Cosmetics Regulation to this kind of products was discarded from the beginning because Regulation (EC) No 1223/2009 on cosmetic products clearly states that it only applies to products which come into contact with the surface of the skin, excluding all ingested, inhaled, injected and implanted products from its scope[25].

3.1.2.1. Policy option MD-1C: Regulation of certain implantable or other invasive products without a medical purpose within the MDD

This option would subject implantable or other invasive products, for which the manufacturer does not claim a medical purpose, to the medical devices legislation provided that they belong

[25] Article 2(2) of Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products, OJ L 342 of 22.12.2009, p. 59.

to a type of products which also exist as a medical device (e.g. body implants, fillers, contact lenses). A positive list would be established and the European Commission would be empowered to manage it. Such a condition would be necessary to avoid an unreasonable broadening of the scope of the medical device legislation to products such as ear-rings or body piercings.

3.1.2.2. Policy option MD-1D: Regulation of certain implantable or other invasive products without a medical purpose outside the legislation on medical devices

This option would keep the scope of the medical devices legislation limited to devices with a medical purpose. It would require the adoption of a separate legislation either in the context of the General Product Safety Directive or a 'standalone' regulation which would set the safety requirements for these products (possibly in analogy to those applicable to similar medical devices).

3.1.3. Reprocessing of single-use medical devices

Based on the findings of the 2010 Commission's report on the reprocessing of medical devices, and with a view to the mandate given to the Commission by Article 12a MDD to submit a proposal deemed appropriate to ensure a high level of health protection, the "no action" needs to be discarded because it would not address the safety concerns identified. Three policy options are reasonably to be considered: the ban on reprocessing of SUD, a harmonized regulation of reprocessing of SUD or some minimum criteria to be respected by Member States that allow the reprocessing of SUD.

3.1.3.1. Policy option MD-1E: Prohibition of the reprocessing of single-use medical devices

The extreme option would be to ban the practice of reprocessing of SUD and their use in the EU, as it is for example the case in France and in Japan.

3.1.3.2. Policy option MD-1F: Harmonized regulation of the reprocessing of single-use medical devices

This option would require the reprocessors of CE marked SUD, be they the users (e.g. hospitals) or external reprocessing companies, to fulfil the same requirements as manufacturers of medical devices and indicate the fact that a device has been reprocessed on the label. Reprocessed SUD would bear the CE marking and would therefore benefit from the principle of free movement of goods. The reprocessing would be limited to CE marked SUD only. The reprocessing of SUD intended for critical use (i.e. intended for surgically invasive medical procedures)[26] would be prohibited due to the risk of infection which may be caused by persistent pathogenic micro-organisms. In addition, Member States would be given the right to ban the reprocessing of SUD and the use of reprocessed SUD on their territory, thus restricting the free movement of reprocessed SUD.

[26] The SCENIHR has based its opinion on three categories of devices depending on risk: non-critical use, semi-critical use and critical use, see Scientific Opinion of the SCENIHR of 15 April 2010, http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_027.pdf and the Commission's report of 27 August 2010, COM(2010)443 final.

3.1.3.3. Policy option MD-1G: Minimum criteria for the reprocessing of single-use medical devices

This policy option would leave it to Member States to ban or to allow the reprocessing of SUD. Should they allow it, they would need to limit the reprocessing to SUD put into service within their territory, to require that reprocessors, be they the users (e.g. hospitals) or external reprocessing companies, fulfill the same requirements as manufacturers of medical devices and reprocessors would have to indicate on the label that the device has been reprocessed. There would be no CE marking of reprocessed SUD and therefore no free movement within the EU.

3.2. Policy options regarding objective MD-2: Appropriate legal requirements taking into account technological, scientific and regulatory developments

3.2.1. Policy option MD-2A: No legislative action

This policy option would maintain the *status quo* and not review the classification rules and essential requirements in order to take account of technological, scientific and regulatory developments. The issues would rather be addressed by legally non-binding guidance.

3.2.2. Policy option MD-2B: Review of the classification rules and essential requirements regarding specific devices or technologies

This policy option would review and adapt, where necessary, the classification rules of the MDD on the basis of discussions which take place in the MDEG Borderline and Classification Working Group and in light of the requests formally submitted to the Commission by Member States in accordance with the MDD.

With regard to nanomaterial, it would incorporate a specific classification rule for medical devices which incorporate or consist of "free" nanomaterial as recommended by the Commission's N&ET Working Group and require manufacturers to provide appropriate information and to take the specific hazards related to the use of nanomaterial duly into account in the context of risk-analysis and risk-management. A definition would be provided on the basis of the Commission Recommendation 2011/696/EU on the definition on nanomaterial.

3.3. Policy options regarding objective MD-3: Enhanced legal certainty and coordination in the field of clinical evaluation and investigations, in particular those conducted in more than one Member State

A full-fledged regulation of clinical investigations similar to the legislation applicable to clinical trials for medicinal products (Directive 2001/20/EC), as well as the possibility of an approval of clinical investigations by an EU body, have been discarded from the beginning because it would not be proportionate to introduce such requirements at EU level for the huge variety of medical devices. However, where appropriate, care should be taken that the Proposal for a Regulation on clinical trials on medicinal products for human use is taken into account also for the rules on clinical investigations on medical devices in order to avoid unjustified discrepancies between two closely related regulatory frameworks.

3.3.1. Policy option MD-3A: Introduction of the term "sponsor" for clinical investigations and further clarification of key provisions in the field of clinical evaluation and investigations

Instead of capturing only clinical investigations carried out by the manufacturer or its authorised representative as currently foreseen by the AIMDD and MDD, this option would introduce the term "sponsor" to cover also clinical investigations for regulatory purposes that are conducted under the responsibility of another person than the manufacturer. This would bring the EU legislation in line with practice in the Member States[27] and at international level. Other key concepts in the field of clinical evaluation and investigations, such as clinical performance, the reporting of serious adverse events and the relationship between clinical investigations and post-market clinical follow-up and other post-market safety issues, would also be further clarified.

3.3.2. Policy options MD-3B – MD-3C: Assessment of multi-national investigations

3.3.2.1. Policy option MD-3B: Coordinated assessment of multi-national investigations by the Member States where the investigation is performed

This policy option would offer to sponsors of multi-national investigations the possibility to submit the application to the Member States concerned simultaneously by means of a single submission. The technical assessment of the application, other than intrinsically national, local or ethical aspects, by the Member States concerned would be coordinated at EU level with one coordinating Member State in the lead (Coordinated Assessment Procedure). Every Member States would remain competent for the final decision regarding the clinical investigation conducted on its territory.

3.3.2.2. Policy option MD-3C: Voluntary cooperation among the Member States where the clinical investigation is performed

This policy option would make provision for facilitating a voluntary cooperation of Member States regarding a sponsor's applications for clinical investigations to be conducted in more than one Member State.

4. ANALYSIS OF IMPACT AND COMPARISON OF THE POLICY OPTIONS

4.1. Impact of policy options MD-1A and MD-1B: (products manufactured utilising non-viable human cells and tissues)

According to policy option MD-1A products manufactured utilising non-viable human cells and tissues, other than those which have undergone only non-substantial modification, which do not principally act by pharmacological, immunological or metabolic means would be submitted to the legislation concerning medicinal products and in particular to the one applicable to ATMP. To the contrary, policy option MD-1B would submit them to the medical devices legislation.

Public health protection and patient safety should be given highest priority when deciding about the appropriate regulatory framework for these products. Provided that appropriate

[27] MEDDEV 2.7/2 (Guide for Competent Authorities in making an assessment of clinical investigation) and MEDDEV 2.7/3 (Clinical investigations: serious adverse event reporting) use already the term "sponsor".

essential requirements are introduced in the MDD addressing possible risks of infection and microbial contamination emanating from non-viable human cells or tissues and that only Notified Bodies with sufficient competence and expertise in the field of tissue engineered products will be able to perform the conformity assessment (see objective 1 of the main part of this impact assessment and the corresponding policy options), public health and patient safety would be protected under the medical devices legislation at a high level which can be considered equivalent to the one assured by a centralised marketing authorisation under the pharmaceuticals legislation. As additional safeguard, a mandatory consultation by Notified Bodies of national authorities that are competent in the field of safety and quality of human tissues and cells in accordance with Directive 2004/23/EC would assure an appropriate evaluation of cell- and tissue-specific risks, notably that the donation, procurement and testing of the cells or tissues have been in line with that directive. Simultaneously, the EMA Committee of Advanced Therapies should be consulted to ensure consistency as regards the possible borderline cases between ATMP and MD.

The economic impact would mainly consist in the time and costs for the manufacturer to bring products manufactured utilising non-viable human tissues or cells onto the market and to comply with the legal requirements in the post-market phase. The length of the approval procedure has both economic impacts on the manufacturers and social impacts, in particular as regards the availability of new and innovative products for patients and users and the attractiveness of Europe as location for innovation.

The main part of this impact assessment (section 4.2) contains a comparison of the typical costs and timelines for approval under the regulations, on the one hand, for medicinal products and, on the other hand, for medical devices. It shows that

- the R&D costs to bring a new medicinal product to the market are significantly higher (€1bn) than the costs to bring a significantly new medical device to the market (€10m);

- the costs for a central marketing authorisation of a medicinal product are significantly higher (€349,500; for SMEs: €263,640) than the costs for a pre-market conformity assessment of a class III medical device (€10,000-€30,000);

- the timeline for the pre-market evaluation is longer for a medicinal product (210 days, without clock-stop) than for a class III medical device (70-105 days, without possible consultation of a regulatory authority).

Comparison of options MD-1A and MD-1B

Options MD-1A and MD-1B can be considered equal in terms of the level of protection of public health and patient safety provided that accompanying measures (additional essential requirements, appropriately qualified Notified Bodies and consultation of competent authorities) are taken. Both would also contribute to reduce the fragmentation of the internal market.

The economic impact of policy option MD-1A is clearly higher compared to option MD-1B. The high costs related to the marketing authorisation under the EU medicinal products legislation (EMA fees, technical requirements and time) has often been criticised and was also mentioned in many responses to the 2008 public consultation. Option MD-1B can thus be considered as the option which would put fewer burdens on economic operators and which

would be more supportive for innovation. Moreover, it would be consistent if devices manufactured utilising non-viable *human* cells or tissues were regulated within the same piece of legislation as devices manufactured utilising non-viable *animal* cells or tissues which are already covered by the AIMDD and the MDD.

Finally, the outcome of the negotiations on the ATMP Regulation and the exclusion from its scope of products which contain or consist of non-viable human cells or tissues and which do not principally act by pharmacological, immunological or metabolic action[28] would support the choice to include these products within the scope of the medical devices legislation.

With a view to the above, option MD-1B is the preferred option and should be retained.

4.2. Impact of the policy options MD-1C and MD-1D (implantable or other invasive products without a medical purpose)

According to policy option MD-1C, products without a medical purpose which are injected or implanted in the human body, or which are otherwise invasive, and which belong to the same category of products that fall within the definition of a medical devices, would be submitted to the requirements of the medical device legislation, provided they are included in a 'positive list'.

With the suggested two-step-approach, the incorporation of a general provision regarding implantable or other invasive non-medical products in the medical device legislation would not have any immediate impact on these products. Only the inclusion in a 'positive list' would trigger the application of the legal requirements regarding a given type of products. This would have the advantage that the concrete impacts on specified products could be assessed once a type of product should be added to the positive list.

Nonetheless, in general terms the expected impacts can already be determined.

For a large part of the products concerned which can be used both for reconstructive (i.e. medical) and aesthetic purposes (e.g. breast implants, wrinkle fillers) nothing will change since most manufacturers of those devices, which are used 'off label' for cosmetic purposes, do claim an intended medical purpose and therefore have to comply with the medical device legislation[29]. Nevertheless, individual cases often cause lengthy discussions with regulatory authorities. The positive impacts of option MD-1C would therefore be that the current situation is legally clarified to the benefit of the internal market and that a loophole would be plugged for those manufacturers who avoid a medical claim.

For other products, option MD-1C would mean a change of the regulatory status. The most common examples are non-corrective contact lenses without medical purpose. Even though some coloured non-corrective contact lenses may also be used as medical prosthesis in case of corneal problems, the vast majority of decorative lenses are used only temporarily to change

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28 See the last paragraph of Article 2(1)(b) of Regulation (EC) No 1394/2007.

29 See the announcement of the French Agency for Health Products AFSSAPS regarding 'produits injectables de comblement de rides' http://www.afssaps.fr/Dossiers-thematiques/Produits-injectables-de-comblement-des-rides/

the eye colour or simply "for fun"[30]. The use of sub-standard contact lenses can lead to corneal ulcers, corneal abrasion, vision impairment and in the worst case blindness[31].

For the manufacturers which produce both corrective and non-corrective contact lenses, the economic impact related to option MD-1C would be negligible since their quality management system anyway must comply with the requirements of the medical device legislation. Manufacturers of only non-corrective contact lenses would have, among others, to draw up a technical documentation (incl. clinical evaluation), be subject to a conformity assessment procedure by a Notified Body and set up a system to respond to incidents (vigilance) which would lead to additional costs. In the case of responsible manufacturers which already today apply an internal quality management system and follow-up of incidents, the additional costs would be limited to the involvement of a Notified Body. Manufacturers which place decorative contact lenses on the market without prior internal quality control and incident follow-up would have to adapt or lose Europe as a market place which would be a desired consequence of this policy option and increase consumer safety.

The enforcement of the requirements applicable to corrective contact lenses, including the control of the quality management of the manufacturer, would enhance the protection of the health of consumers compared to which the additional costs are to be considered low. The same considerations would apply to other aesthetic implantable or injectable devices which can cause infections, allergies, wounds, or skin damages[32].

Option MD-1C would also be in tune with regulations of major trading partners. In the US and Japan, the medical devices regulations explicitly cover contact lenses which include non-corrective ones and the US FDA approved cosmetic wrinkle fillers under their medical device regulations.

The application of the medical device legislation to implantable or other invasive products without a medical purpose may force some products out of the market in case that the manufacturer cannot demonstrate conformity with the essential requirements based on clinical data. In particular, those manufacturers who cannot rely on clinical data obtained for medical devices of the same category would, for ethical reasons, unlikely be allowed to conduct a clinical investigation with a product that does not have a medical purpose. Such effect, however, would ensure that only those non-medical products would be allowed on the EU market for which the manufacturer can prove the same level of safety and performance as for a similar medical device for which the demonstration of the conformity with the essential requirements by means of clinical data is required by law.

Policy option MD-1D, on the contrary, would seek a solution outside the medical devices legislation and would require the adoption of a 'standalone' legislation. It can be assumed that, if adopted, such legislation would achieve an equivalent level of health protection as the

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30 See also US FDA's alert "Improper use of decorative contacts may haunt you" (Oct. 2009), http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm048902.htm

31 According to a study in France, wearing cosmetic contact lenses increases 16.5. times the risk of developing microbial keratitis, *Sauer A./Bourcier T.*, Microbial keratitis as a foreseeable complication of cosmetic contact lenses: a prospective study, in: Acta Ophtalmologica 2011, 1. According to the findings of the CLEER project, coloured contact lenses (plano and powered) resulted in statistically significantly more events than normal powered contact lenses, see *Schweizer H.*, et al. The European Contact Lens Forum (ECLF) – The results of the CLEER-Project, in: Contact Lens & Anterior Eye (2011), doi:10.1016/j.clae.2011.02.013.

32 See also US FDA's alert "Wrinkle relief: injectable cosmetic fillers" (June 2008), http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm049349.htm

medical device legislation and contribute to the good functioning of the internal market. An argument in favour of a separate legislation for aesthetic implants and other invasive products is to maintain the medical device legislation limited to products which have a medical purpose and which inherently are subject to a risk/benefit analysis. It would also be easier to extend the scope of such a 'standalone' legislation to other aesthetic products which have no similarities to medical devices.

The negative impact of a separate legislation would be that manufacturers which produce same or similar products with and without a medical purpose (e.g. corrective and non-corrective contact lenses without medical purpose) would be subject to two different product-related legislations which, in particular for SME, would be more burdensome and increase compliance costs. Moreover, it would not appear logical to submit products which have the same features and the same risk profile to different requirements. In addition, experiences gained under one legislation (e.g. vigilance reporting) could not be easily taken into account for regulatory purposes for products subject to another legislation.

Comparison of policy options MD-1C and MD-1D

Due to the above demonstrated advantages, in particular in terms of consistency and competitiveness, of a regulation of certain implantable and other invasive products without a medical purpose within the medical devices legislation, policy option MD-1C is the preferred option and should be retained.

4.3. Impact of the policy options MD-1E and MD-1G (reprocessing of single-use medical devices)

Despite the 2010 Commission report, no definitive information on the size of the market of reprocessed SUD is available[33]. It is in particular impossible to gather meaningful data regarding 'in house' reprocessing of SUD by the users due to legal uncertainty and liability aspects. Most of the data available concern Germany since it has the most developed regulatory framework for the reprocessing of SUD. According to those data, mainly invasive and complex SUD used in interventional cardiology (e.g. catheters) are reprocessed by external reprocessing companies.

According to data provided by the European market leader of external reprocessing companies, it reprocesses around 230,000 SUD a year, practically all of them being invasive devices, and employs 140 staff in the field of SUD reprocessing.

Economic considerations are the main drivers for reprocessing of SUD. They need to be compared to the social implications of this practice (safety and ethical aspects). Environmental aspects (e.g. reduction of medical waste) should also be considered.

Economic aspects:

Increasing resource constraints require cost-containment in healthcare. The reprocessing of SUD is seen as a possibility of dividing purchasing costs for expensive SUD over multiple patients. According to a cost-effectiveness analysis provided to the Commission by the reprocessing industry, the German reprocessing companies set the prices for reprocessing at

[33] Also the 2008 GOA report on reprocessing of SUD could not provide information about the size of the US reprocessed SUD market.

between 15% and 50% of the prices for new devices, depending on the product type[34]. The before-mentioned analysis in respect to the German market estimates potential cost-savings for cooled and non-cooled high-frequency (HF) ablation catheters used in cardiology at around 23mio.€ in Germany and extrapolates this data to 83mio.€ for Europe. This study is based on the assumption that ablation catheters are reprocessed 4 times and that 70% of the devices are reprocessable.

However, the overall cost-effectiveness of SUD reprocessing, when taking into account all costs linked to the reprocessing process, including validation processes and liability costs in case of failure of a reprocessed SUD, is disputed. It appears that the calculation of the costs is often not well described and it is not clear if costs for the validation of the feasibility of reprocessing of a given SUD as well as the reprocessing process to ensure an acceptable level of safety of a reprocessed SUD are taken into account (e.g. functionality and biocontamination aspects). Other important elements such as the cost of potential adverse events for patients, costs of the facilities, consumption of water or energy do not seem to be taken into account either. The cost-effectiveness may also vary considerably depending on the number of SUD reprocessed per year (scale effect) and the existence of a quality management system.

The cost-effectiveness analysis for the German market does not seem to take into account the validation process regarding the number of possible reuses. The assumption of four reprocessing cycles is an estimate based on the common clinical practice, but there is no scientific evidence that this number might be achieved for all HF ablation catheters and that the reprocessed SUD achieves the same level of safety and performances as the new device. In addition, there is no indication that the reprocessing costs might be extrapolated to the whole Union.

A study performed in Belgium[35] points out that the cost of reprocessed SUD angiography catheters may be higher than the cost of new products when the same level of safety and quality is ensured, i.e. when the reprocessor needs to demonstrate that the requirements of Directive 93/42/EEC are fulfilled. This study underlines that without scale benefits and taking into account the cost of an estimate rate of adverse events, the reprocessing costs are generally higher than or equivalent to the purchase of new SUD.

The need of scale effect to achieve cost-effectiveness is also one of the main conclusions of another study[36] which states that cost saving depends on the number of devices used per year in a cardiological department as well as the development of prices for new devices. For a hospital with a median number of 600 angioplasties and 200 electrophysiological studies per year, the study calculates cost-savings of 12% for percutaneous coronary angioplasty (PTCA) catheters and 33% to 41% for electrophysiology and ablation (EP) catheters. But this study is not based on real costs but on a mathematical model.

An additional economic argument brought forward in favour of SUD reprocessing is the competitive pressure on original SUD manufacturers and its impact on prices for new devices.

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34 *Von Eiff W.*, Reprocessing of single-use medical devices, Münster 17.2.2011.

35 *Larmuseau D.* et al., The impact of reprocessing single use devices in Belgium - An economic study, Erasmus MC University Medical Center, Institute for Medical Technology, Rotterdam, Netherlands, April 2008 (not published).

36 *Tessarolo F.* et al. Critical issues in reprocessing single-use medical devices for interventional cardiology.

On the other hand, a broader use of the reprocessing practice would lead to a decrease of the sales volumes of original devices and therefore to a potential increase of their prices.

Finally, an independent scientific literature review on the economic analysis of SUD reprocessing published in 2008[37] comes to the conclusion that the evidence on the cost-effectiveness of this practice is considered inconclusive and not established.

Public health and safety considerations:

The number of documented incidents regarding reprocessed SUD is very small although it cannot be excluded that the reporting of incidents clearly linked to a reprocessed SUD is incomplete due to lack of knowledge about the fact that the device was reprocessed or due to liability aspects. In the US, available data did not show evidence of a significantly increased risk to patients exposed to reprocessed SUD[38]. This may be due to the requirements imposed by US FDA regulation on the reprocessing of SUD but there may also be a "grey" area where an incident cannot be clearly established or linked to the reprocessed SUD.

The scientific opinion issued by SCENIHR in 2010 on the safety of reprocessed single-use devices[39] describes biological risks for patients exposed to reprocessed SUD especially linked to viruses and non-conventional transmissible agents (prions). It also refers to publications which indicated that SUD having undergone reprocessing do not meet the same quality standards as new devices delivered by the original manufacturer since reprocessed SUD may exhibit contaminations by proteins and viral nucleic acids. A specific hazard, as highlighted in the SCENIHR opinion, is the possible contamination with agents causing transmissible spongiform encephalopathies (TSEs) such as variant Creutzfeldt-Jakob disease (vCJD). Medical devices may become contaminated with prions after contact with infected tissues and/or blood. Prions are particularly resistant to commonly used physical and chemical methods of cleaning, disinfection and/or sterilization and only relatively aggressive cleaning methods, not compatible with the commonly used materials for SUD, can ensure their inactivation.

Other major hazards described by SCENIHR are the persistence of chemical substances (e.g. ethylene oxide and its potentially toxic reaction products) used during the reprocessing process and the alterations in the performance and functionality of the SUD due to the reprocessing process. It is clear that not all SUD can be reprocessed due to their characteristics or their complexity. According to data provided by a reprocessing company[40], among 9,770 highly complex single-use medical devices assessed for their suitability to reprocessing, 6,030 (62%) were not reprocessable and among those, around 50% are not suitable for reprocessing for technical reasons. A validation process is therefore needed in order to ensure that the reprocessing of the SUD does not endanger the patient's safety.

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37 *Jacobs P.* and al., Economic analysis of reprocessing single use medical devices: a systematic literature review, in: Infect Control Hosp Epidemiol 2008;29:297-301.

38 See the Jan. 2008 report of the United States Government Accountability Office (GOA) on Reprocessed single-use medical devices,

39 SCENIHR opinion "Safety of reprocessed medical devices marketed for single use" http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_027.pdf.

40 *Matthias Tschoerner,* Reprocessing in practice. Presentation given in vDSMH-EAMDR Forum on "Reprocessing of highly complex medical devices", 28. November 2008, Artemis Hotel, Amsterdam.

For the above public health and safety considerations, reprocessing of SUD, if allowed, would need to be subject to a demonstration by the reprocessor that the benefit/risk ratio of the reprocessed SUD is the same than the one of a new SUD. In addition, ethical concerns also need to be taken into consideration with regard to information of the patient and of the healthcare professionals about the potentially increased risk linked with the use of a reprocessed SUD (e.g. patient's informed consent, information to healthcare professionals).

Environmental aspects:

Finally, the potential impact of SUD reprocessing on the environment should be considered. Mostly, the argument of medical waste reduction is brought forward in favor of reprocessing[41]. The reduction of waste, however, is only one (positive) environmental impact which may be reduced by (negative) impacts caused by transport, consumption of water, energy, disinfectants or chemicals (e.g. ethylene oxide[42]). To date, there does not seem to be a study available taking into account the global environmental impact of the SUD reprocessing practice. Results from a study comparing the environmental impact of single-use nappies versus reusable nappies, performed by the UK environmental agency, might however give some indications in that respect[43]. The conclusion of this study comparing disposable nappies, home laundered flat cloth nappies and commercially laundered prefolded cloth nappies delivered to the home was that no significant difference between the three practices as regards environmental impacts could be established.

Due to the inconclusiveness of a potential positive environmental impact of SUD reprocessing, environmental considerations should not play a determining factor in the assessment of the policy options which will be developed in the following paragraphs.

A ban on SUD reprocessing (policy option MD-1E) would be the safest option in terms of public health and patient safety because it would exclude all possible risks and hazards linked to the SUD reprocessing practice, including transmission of viruses and non-conventional transmissible agents (e.g. prions responsible for vCJD). On the other hand, a ban on the SUD reprocessing could lead to some pressure on some national healthcare budgets and might limit the access of patients to certain expensive interventional procedures in some Member States due to the prices of original medical devices. Limited availability of certain medical devices may therefore be a downside of a ban in terms of public health and patient safety.

As regards the economic impact, option MD-1E would have a negative economic impact since it would mean the end of the third party SUD reprocessing industry in Europe. It would also legally prohibit the 'in house' reprocessing of SUD by hospitals. Benefits from a ban could possibly be drawn by the original SUD manufacturers since their sales volume would probably increase in some Member States.

Policy option MD-1F (harmonized regulation of SUD reprocessing) would have some negative economic impact on the SUD reprocessors since they would likely need to enhance their validation process in order to meet regulatory requirements applicable to original equipment manufacturers and the additional labeling requirement to indicate that the device has been reprocessed. However, the association of US reprocessing companies claims that

41 New York Times, 5.7.2010: "In a world of throwaways, making a dent in medical waste"; Kwakye G. et al., Green Surgical Practices for Health Care, in: Archives of Surgery, 146 (no. 2), Feb. 2011, p. 131.

42 Classified as carcinogenic according to WHO.

43 Environmental agency, Life Cycle Assessment of Disposable and Reusable Nappies in the UK. www.environment-agency.gov.uk.

their members would already meet these requirements. This impact would be balanced with the potential that this option may provide in terms of further development of this activity across Europe by means of creating a single market for reprocessed SUD (except for SUD intended for critical use and for those Member States which would impose a ban of SUD reprocessing). This may also lead to the creation of jobs in the reprocessing industry, even though the number of new jobs is likely to be relatively low. A negative impact may also be a foreseeable decrease of the sales volumes for original SUD manufacturers, with some potential lose of jobs in the manufacturers' facilities.

The fact that reprocessors would be considered as manufacturers would ensure a high level of safety because any reprocessed SUD would need to have the same risk-benefit ratio as a new SUD. In addition, an acceptable level of protection of public health and patient safety against the potential risk of transmission of diseases (e.g. vCJD) would be ensured by means of a ban of the reprocessing of SUD intended for critical use. Individual Member States could prohibit the reprocessing of SUD and their use on their territory which would allow addressing specific situations that some Member States may have with regards to the reprocessing of SUD.

Policy option MD-1G (minimum requirements to be respected by Member States allowing SUD reprocessing) would have the smallest impact compared to the current situation. The economic impact on reprocessors might be caused by stricter validation processes in order to meet requirements applicable to original medical devices manufacturers and the additional labeling requirement to indicate that the device has been reprocessed. As stated above, the association of US reprocessing companies claims that their members would already meet these requirements. But reprocessors (except for those in larger Member States) would likely not be able to benefit from scale effects since they would only be allowed to reprocess SUD put into service in their own Member State and to put them back into the use cycle in that same Member State.

In terms of public health and patient safety, by requiring reprocessors to meet the same requirements as manufacturer, this option would enhance the protection of patients in comparison with today's situation. This option would also address specific situations of Member States prompting them to ban SUD reprocessing and would contribute to address ethical concerns that some Member States may have with regard to the reprocessing of SUD.

Comparison of policy options MD-1E to MD-1G:

An EU-wide ban on SUD reprocessing (option MD-1E) would have the most far-reaching consequences as regards the impact on the (relatively small) reprocessing industry and on some national healthcare budgets. Whilst the ban could be justified invoking the precautionary principle, it may also have a negative impact on public health and patient safety by reducing access to expensive devices in some Member States. It therefore does not appear as the most appropriate option.

Option MD-1G could be considered as the smallest common denominator for EU legislation. It would enhance patient safety in comparison with today's situation. Option MD-1G would however ensure a lower level of public health protection than policy option MD-1F due to the possibility to reprocess also SUD intended for critical use. Finally, option MD-1G would not enable SUD reprocessors to reach large scale business activity and may prevent SUD

reprocessing in smaller Member States where this practice would not be economically viable (no scale effect). This option therefore does not appear the most appropriate either.

A harmonized regulation of SUD reprocessing (option MD-1F) with the possibility for Member States to ban the practice appears the preferred option and should be retained. It would ensure a high level of public health protection and patient safety. At the same time, the SUD reprocessing industry would be able to develop economies of scale at high standards. This may ultimately also have a positive impact on some national healthcare budgets. Ethical aspects (information of the patient and of the healthcare professionals) would be addressed due to the labeling requirement.

4.4. Impact of the policy options MD-2A and MD-2B (appropriate legal requirements taking into account technological, scientific and regulatory developments)

Option MD-2A would not lead to any regulatory change regarding medical devices using material or technologies with an increased risk (e.g. medical devices with nanomaterial; ingested devices; assisted reproductive technologies; agents for organ conservation; apheresis systems; products incorporating living microorganisms). Legal uncertainty caused by different interpretations and implementation practices in the Member States and obstacles to the free movement of goods would continue to exist leading to different levels of protection of public health and patient safety. Manufacturers would not be obliged to take into account specific hazards emanating from a specific device type (e.g. ingestion of an absorbable substance). Especially in the field of nanotechnology, such approach would disregard scientific[44], political[45] and regulatory[46] developments of the last years which favour a proactive approach in this matter.

Option MD-2B, to the contrary, would make legislative adaptations to the current requirements in the field of classification and essential requirements where necessary. The number of products would be limited since they would mainly concern products which have traditionally not been considered as medical devices (e.g. some ingested products) or which have been emerging only recently. As regards devices using nanomaterial, specific essential requirements and a classification rule regarding devices using "free" nanomaterial[47] would ensure that the benefits and risks linked to the use of nanotechnology are appropriately addressed by the legislation and provide an appropriate basis for developing, if appropriate, additional specifications for the risk-assessment and risk-management to be followed by the manufacturers as scientific knowledge about nanotechnology evolves. The economic impact would be insignificant since devices currently using "free" nanomaterial are likely to fall within class III devices due to other product characteristics. Since nanotechnology usually is part of the specific performance of the medical device, the information is also already provided by the manufacturer. Option MD-2B would make the medical device legislation

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44 SCENIHR, "Scientific basis for the definition of the term 'nanomaterial'", 8.12.2010; JRC, "Considerations on a definition of nanomaterials for regulatory purposes", June 2010.

45 Draft Commission Recommendation on the definition of the terms "particulate nanomaterial" and "nano-constituent material", not yet adopted.

46 Regulation 1223/2009 on cosmetic products was the first product legislation containing provisions regarding nanomaterial.

47 Medical devices incorporating or consisting of nanomaterial unless it is encapsulated or bound in such a manner that it cannot be released to the patient's organs, tissues, cells or molecules should be classified in class III.

future-proof when other devices come to the market which use nanomaterial in a less transparent way or which otherwise would belong to a lower risk class.

For the above reasons, option MD-2B is the preferred option and should be retained.

4.5. Impact of the policy options MD-3A to MD-3C (clinical investigations and evaluation)

Option MD-3A would not have any negative impact because the vast majority of Member States already use the internationally defined term "sponsor"[48] instead of manufacturer/authorised representative and submit them to the legal requirements applicable to clinical investigations.

This option would therefore have the positive impact of harmonising the practice throughout the EU. It would also be a pre-condition for enhancing the cooperation between Member States as regards the technical assessment of applications for clinical investigations. Legal clarification of other concepts such as "serious adverse event" and "post-market clinical follow-up", currently further explained in guidance documents, will also have the positive impact of harmonising the practice throughout the EU.

For these reasons, option MD-3A is necessary for any effective implementation of the requirements regarding clinical investigation and evaluation as it will ensure legal certainty and uniform application of the rules. It should therefore be retained in any case as *condition sine qua non* complementary to any of the two alternative options regarding more coordination of the assessment procedure.

Options MD-3B and MD-3C concern the procedure and the question to which extent Member States should coordinate the assessment of aspects related to the safety of the investigational device. As it was stated in the problem description, no exact data exist as regards the number of multi-national clinical investigations, but the number can be estimated at around 200-350 a year which, in principle, would qualify for such a coordinated assessment.

Option MD-3B would bring most benefit for manufacturers (sponsors) who, by means of a single submission, could avoid multiple submissions and therefore reduce administrative burden. Industry, however, could not provide data as regards the costs caused by individual submissions and therefore, the administrative burden reduction cannot be quantified. Moreover, sponsors would benefit from consistency in the outcome of the technical assessment when this is coordinated. The option would nevertheless leave to the sponsor the choice between a single submission and multiple applications. This option would thus avoid to 'force' multi-national investigations into a coordination procedure where this might not be suitable due to the specific circumstances of the case. A coordinated procedure would also contribute to the objective that patients subject to the clinical investigation are protected at the same high level in all Member States where the investigation is conducted. Finally, a coordinated assessment procedure would not interfere in the Member States' ultimate responsibility for the approval of an investigation on their territory and thus respect the subsidiarity principle. Especially for smaller Member States, it would bring the benefit that resources could be shared and duplication of assessment of the same documentation by several authorities be avoided.

[48] ISO 14155:2011: Clinical investigation of medical devices for human beings – Good clinical practice.

A coordinated assessment procedure, however, would have an impact on the EU budget because an EU body (Commission or an agency) would need to provide the administrative support to the national competent authorities in the coordination of the assessment. This would include the setting up of an IT infrastructure which would allow sponsors to file a single submission which is simultaneously forwarded to all Member States concerned and to facilitate the coordination between the national authorities where needed. In terms of human resources, 5 FTE at EU level would be required to implement option MD-3B.

Option MD-3C would be less ambitious and leave the participation in a coordinated assessment to the willingness of each individual Member State. The costs at EU level would be the same for the IT infrastructure allowing for single submission and coordination between volunteering Member States. But since coordination would be voluntary, less human resources would likely be needed to facilitate the coordination, possibly only 1 FTE at EU level.

The advantage of a voluntary coordination would be that only those Member States that are committed to take the coordinated assessment into account for the national approval of the clinical investigation would participate in such a process. This would likely enhance the effectiveness of the coordination when it takes place. The disadvantage, however, would be that participation in the coordination would be left to the willingness of the national competent authorities. The benefits for manufacturers (sponsors) of multi-national investigations would therefore be lower compared to the previous option. More importantly, the level of protection of patients participating in multi-national investigations would not be harmonised EU wide.

Comparison of policy options MD-3B to MD-3C:

Between policy options MD-3B and MD-3C, option MD-3B is the preferred one and should be retained. It would be an effective and efficient means to achieve an enhanced level of coordination as regards clinical investigations conducted in several Member States for the benefit of patients and sponsors. The benefits of option MD-3C would be uncertain because it would depend on the Member States' willingness to participate or not. Giving the sponsors the possibility to request coordination between the competent authorities involved appears to be the best solution, on the one hand, to achieve a positive impact of such coordination and, on the other hand, avoiding forcing such coordination where it would not fit due to the specificities of the investigation plan.

Since the Clinical Trials Directive in the field of pharmaceuticals is currently also being revised, the developments in that field are being followed to ensure consistency in the approach of both initiatives, unless differences are justified by the specificities of the sectors.

5. OVERVIEW OF PREFERRED OPTIONS

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

- Option MD-1B: Regulation of products manufactured utilising non-viable human cells and tissues as medical devices

- Option MD-1C: Regulation of certain implantable or other invasive products without a medical purpose within the MDD

- Option MD-1F: Harmonized regulation of the reprocessing of single-use medical devices

- Option MD-2B: Review of the classification rules and essential requirements regarding specific devices or technologies

- Option MD-3A: Introduction of the term "sponsor" for clinical investigations and further clarification of key provisions in the field of clinical evaluation and investigations

- Option MD-3B: Coordinated assessment of multi-national investigations by the Member States where the investigation is performed.

The policy options suggested for the extension of the scope of the MDD and its review on the basis of technological, scientific and regulatory developments would not lead to significant cost increases. On the other hand, filling the regulatory gaps regarding products manufactured utilising non-viable human cells and tissues, aesthetic products and reprocessing of single-use devices as well as introducing specific requirements for certain nanotechnology-based devices would address politically sensitive issues and eliminate uncertainties and divergences between the Member States.

As regards the suggestion to establish a coordinated assessment procedure for multi-national clinical investigations, it would be an important step towards a more harmonised implementation of the requirements and would reflect parallel regulatory developments with regard to clinical trials in the field of pharmaceuticals.

6. MONITORING AND EVALUATION

To monitor and evaluate the implementation of the future legislative act concerning medical devices (other than IVD) in respect to the specific issues discussed in this Annex 1, the following indicators can be taken into account:

6.1. Scope

6.1.1. Products manufactured utilising non-viable cells or tissues of human origin

The chosen policy option shall lead to the disappearance of the regulatory gap at EU level with regard to certain products manufactured utilising non-viable human tissues or cells and to a clear distinction between the application of Directive 2004/23/EC on tissues and cells, Regulation 1394/2007 on ATMP and the future medical device legislation. An indicator of success will be the creation of an internal market of these products in accordance with high safety standards.

6.1.2. Implantable or other invasive products without a medical purpose

The chosen policy option shall lead to the disappearance of regulatory uncertainties with regard to the regulation of implantable or other invasive products without a medical purpose which are similar to medical devices. Its successful implementation should lead to the

reduction of the number of such products available on the market that do not meet the safety and performance requirements set out in the medical device legislation.

6.1.3. Reprocessing of single-use medical devices

Harmonised requirements regarding the reprocessing of SUD (with the possibility for Member States to prohibit it) should lead to the development of a high quality and strictly regulated reprocessing sector in the EU in the field of single-use medical devices. Indicators to monitor the success of the chosen policy options are: the impact of an EU-wide regulation of SUD reprocessing on national healthcare budgets and the number of vigilance cases related to reprocessed SUD.

6.2. Review of the classification rules and essential requirements regarding specific devices or technologies

The chosen policy option shall reduce the number of controversial cases as regards the appropriate classification of a given medical device and the essential requirements applicable to it.

6.3. Coordinated analysis of clinical investigations conducted in more than one Member State

Indicator of success of the chosen policy options in the field of clinical investigations and evaluation will be the number of sponsors' single submissions and the coordinated technical analysis of the safety aspects of the investigational device. Part of the evaluation of the success of this new procedure should be the benefits for national competent authorities in terms of work-sharing and the length of approval time of applications which went through a coordinated assessment procedure after single submission compared to those which are submitted individually in several Member States.