Results of the public consultation on SCENIHR's preliminary Opinion on Guidance on the Determination of Potential Health Effects of Nanomaterials Used in Medical Devices

A public consultation on this Opinion was opened on the website of the Scientific Committees from 18 July to 03 October 2014. Information about the public consultation was broadly communicated to national authorities, international organisations and other stakeholders.

11 organisations and individuals participated in the public consultation providing 110 comments to different chapters and sections of the Opinion. Each submission was carefully considered by the SCENIHR and the scientific Opinion has been revised to take account of relevant comments. The literature has been accordingly updated with relevant publications. The scientific rationale and the Opinion section were clarified and strengthened.

The SCENIHR thanks all contributors for their comments and for references sent during the public consultation.

The table below shows all the comments made about each of the questions posed in the Opinion and SCENIHR's response to them. It is also indicated if the comment resulted in a change of the Opinion.

SUBMISSIONS				SCENIHRs Response
No	**Name of individual/ organisation**	**Table of content to which comment refers**	**Comment**	**SCENIHRs Response**
1	Berzanskis Laurel, Health Care Without Harm Europe, laurel.berzanskis@hcwh.org, Belgium	ABSTRACT	Line 4- 9 - Limiting the definition of nanomaterials to a range of between 1 nm and 100 nm is inappropriate. The biological behaviour of materials between 100 nm and 1000 nm (in one, two or three dimensions) can also pose novel risks, as at this scale they may share many of the characteristic behaviours of nanomaterials below 100 nm in size. These shared properties may include very high reactivity, bioavailability, increased influence of particle surface effects, strong particle surface adhesion, strong ability to bind proteins and very high bioavailability. Attached articles: Magrez A, Kasa S, Salicio V, Pasquier N, Won SJ, Celio M, et al. Cellular toxicity of carbon-based nanomaterials. Nano Letters.2006;6(6):1121-5. Higaki M, Ishihara T, Izumo N, Takatsu M, Y. M. 2005. Treatment of experimental arthritis with poly(D, L-lactic/glycolic acid) nanoparticles encapsulating betamethasone sodium phosphate. Annals of the Rheumatic Disease.2005;64:1132-6.	SCENIHR agrees with the comment that also for particles with sizes above 100 nm the physchem properties may change (see also the SCENIHR Opinion on the Scientific Basis for the Definition of the Term "Nanomaterial". (SCENIHR 2010). However, the Recommendation for the definition of a nanomaterial that is currently included in several European Regulations (e.g. for cosmetics, for biocides) specifically designates a nanomaterial as particles with a size between 1 and 100 nm (Commission Recommendation of 18 October 2011 on the definition of nanomaterial , 2011/696/EU). Also in the new proposal for regulation of medical devices this definition of the recommendation is included (COM(2012) 542 final, Brussels, 26.9.2012). It should be realised that when performing a risk assessment of the use of particles in a medical device, however, it is possible to apply the text as mentioned in the Opinion also for particles with a size larger than 100 nm.

			Wagner V, Dullaart A, Bock A-K, Zweck A. The emerging nanomedicine landscape. Nature Biotechnology.2006;24(10):1211-8. Junghanns J-UAH, Müller RH. Nanocrystal technology, drug delivery and clinical applications. International Journal of Nanomedicine. 2008;3(3):295-309. SCENIHR – Opinion on: Scientific Basis for the Definition of the Term "nanomaterial" 8 December 2010doi:10.2772/39703	Text has been added to the Abstract. "It should be noted that when performing a risk assessment of the use of particles in a medical device, however, it is possible to apply this Guidance also for particles with a size larger than 100 nm." Also SCENIHR is aware that similar to the examples indicated in the provided literature, EMA uses a broader definition for nanomedicines being particles with sizes below 1000 nm (see EMA website).
2	Berzanskis Laurel, Health Care Without Harm Europe, laurel.berzanskis@hcwh.org, Belgium	ABSTRACT	Lines 4-9 - Some nanomaterials used in medical products do not fall neatly in the size definition of nanomaterials of approximately 1-100 nm. Nanomaterials being developed for a variety of clinical applications include liposomes measuring 100- 200 nm, nanoshells measuring 60-400 nm and drug delivery systems measuring 100- 200 nm. A recent survey of nanomedicine products noted that most were sized up to 300 nm, but that some were even larger. Attached article: Etheridge, M. L. et al. The big picture on nanomedicine: the state of investigational and approved nanomedicine products. Nanomedicine: Nanotechnology, Biology and Medicine 9, 1-4 (2013).	SCENIHR agrees with the comment. See also response to previous comment. However, it is noted that you are including medicinal products in your examples. Please note that this Opinion refers to medical devices only. Medicinal products were not included in the ToR and are outside the mandate of the SCENIHR
3	Berzanskis Laurel, Health Care	ABSTRACT	Line 15-25 - Other relevant examples include in vitro tests using biosensors to specify	The Opinion discusses medical devices. The example mentioned in the comment, is for an in vitro

	Without Harm Europe, laurel.berzanskis@hcwh.org, Belgium		molecules associated with a specific disease (biomarkers) e.g., detection of with medical devices. The fheart disease via DNA coaterd gold nano particles combined with biosensor chip to read protein values. Active drug delivery, such as nanocapsules equipped with molecular antennae, are injected into the patient. If the nanocapsules come intexample is an In vito contact with certain disease structures, then the content of the capsules are released. Article attached: Walhout, B. et al. Nanomedicine in The Netherlands: social and economic challenges. The Hague, Rathenau Instituut (2010).	diagnostic medical device which is not discussed in the document. SCENIHR recognises the existence of such devices but considers that such devices pose a different risk than the medical devices discussed in the Opinion as in general for an in vitro diagnostic medical device there is no patient contact with the device, as explained in the introduction of the Opinion. Only biosensors having contact with patient tissue are considered in the Opinion. No action needed.
4	Stock Gregor, FIDE - Federation of the European Dental Industry, g.stock@fide-online.org, Germany	ABSTRACT	In line 22 the exposure to the nanomaterial is mentioned as well in line 41 the „potential release“, and in line 23-25 the generation of nanoparticles independent if the device contains such particles or not; however, in the abstract it is only discussed that the use of nanomaterials must be evaluated, that imply the evaluation of the nanoparticles included in the formulation of the device independent of their release. In our Opinion it is much more important for the safety evaluation of a medical device to evaluate any released nanomaterial (independent if added to the product or formed during its use) instead to characterize and evaluate the	SCENIHR agrees with the comment. This aspect is addressed in line 23 – 25 of the abstract in which this aspect is brought to the attention of the reader. The potential release of nanoparticles is indicated even when nanomaterials are not used by the production of a medical device. It is clear that the material released should be analysed. No action needed.

			nanomaterials added to the product.	
5	Sanak Aleksandra, Council of European Dentists (CED), ced@eudental.eu, Belgium	ABSTRACT	Lines 14 - 23: dental filling materials are listed uner free nanomaterials in paste-like formulations. However, this only is the case for materials in the non-set state. In the mouth they are set and then the nanoparticles are not free anymore. Therefore, this should be adjusted in order to prevent confusion. Lines 23 - 25: The CED shares SCENIHR's Opinion that medical devices not containing nanomaterials can generate nanoparticles as a result of wear-and-tear. The approaches indicated in the preliminary Opinion may also be applicable for such wear-and-tear generated nanoparticles. Lines 34 - 36: The CED welcomes the reference to ISO 10993-1:2009. Lines 34 - 41: The risk assessment should be performed on a case-by-case basis, for each specific medical device containing nanomaterials.	Lines 14 – 23: SCENIHR agrees with the comment. This aspect is discussed in the risk assessment of dental materials in section 3.5.1. In the abstract just a general indication is presented of the types on medical devices that contain nanomaterials. No action needed. Lines 23 – 25. No comment. Lines 34 – 36. No comment. Lines 34 – 41. A risk assessment is needed for every medical device so this is already a case-by-case approach. No action needed.
6	Prina-Mello Adriele, Trinity College Dublin / ETPN, prinamea@tcd.ie, Ireland	ABSTRACT	INTRODUCTION TO THE READER: In adherence to the guidelines for the submission of contributions in the frame of the public consultation process, ETP Nanomedicine has prepared the following document where we would like to bring point-by-point comments to the documents. A sub-committee of the ETPN Working Group in Toxicology and Characterization lead by	 Answers to ETPN comments Final.docx

			Dr. Prina-Mello from Trinity College has acquired (or had already) all the necessary background information and from there they carefully addressed all the section of this Guidance document. In details please see our comments and Opinions to be revised through this consultation process in the here enclosed document. This document covers all chapters and section of the Guidance document and it is divided as requested.	
7	FLAMENT Guillaume, Nanotechnology Industries Association (NIA), guillaume.flament @nanotechia.org, Belgium	ABSTRACT	This Guidance addresses nanomaterials used in medical devices on the basis that they 'pose a challenge for the safety evaluation and risk assessment of these medical devices'. Nanomaterials are nevertheless 'similar to normal chemicals/substances in that some may be toxic and some may not' [1]. Nanomaterials with no toxicological issues should be excluded from the scope of this Guidance (e.g. liposomes). In principle the described methodology is a realistic approach to determine adverse effects by a case-by-case and step-by-step approach. Nanosilver particles are not used as free nanoparticles but embedded in the material; anti-microbial silver ions are released. [1] European Commission, Communication on the Second Regulatory Review on Nanomaterials, COM/2012/0572 final	Liposomes are not considered medical devices. They are primarily used for drug delivery and are regulated (when used for drug delivery) by EMA. EMA has published a reflection paper on the use of liposomes for drug delivery addressing specifically generic preparations. (EMA, 2013, document: EMA/CHMP/806058/2009/Rev. 02). This is not part of the ToR for this Opinion and outside the mandate of the SCENIHR For all medical devices a risk assessment has to be performed even when it contains non-toxic materials. SCENIHR agrees that the activity of silver nanoparticles is mainly due to ion release. However, not all nanosilver that is used is embedded in a matrix, e.g. in wound dressings.

8	Berzanskis Laurel, Health Care Without Harm Europe, laurel.berzanskis@hcwh.org, Belgium	1. BACKGROUND	Page 7, line 8-16 - Other diagnostic applications using nanotechnology and already on the market include: colloidal gold particles which, due to their stability, have been widely used to rapidly test for pregnancy, ovulation, HIV and other indications; magnetic nanoparticles used for cell sorting applications in clinical diagnostics; and superparamagnetic iron oxide nanoparticles for magnetic resonance imaging first approved in Europe in 1993. See attached article: Wagner, V. et al. The emerging nanomedicine landscape. Nature Biotechnology 24, 1211-1218 (2006).	The background is text provided by the European Commission formulating the questions for the SCENIHR mandate. As such the background cannot be changed by the SCENIHR. The examples indicated in the comment are partly in vitro applications of nanomaterials, which are not considered in the Opinion (see also response to comment nr.3). Contrast agents used to enhance the diagnostic results of medical imaging are regulated as medicinal products and thus outside the scope of this Opinion. No action needed.
9	King Mel, Medicines and Healthcare products Regulatory Agency (MHRA), UK, mel.king@mhra.gsi.gov.uk, United Kingdom	1. BACKGROUND	Overall comment: like so many areas associated with devices this will grow and grow. Implications for NBs and CA expertise and capacity – realise this might be part of negotiations with government leaders rather than response to this document. Also needs to be partnership vigilance with speciality groups as new technologies are introduced/followed up. As alluded to by other people assessing this document it is not evident what the reason was for only focusing on medical devices. There appears to be significant crossover between devices and medicines in particular the increasing numbers of combination devices. It would seem prudent to include	The background and terms of references is text provided by the European Commission when formulating the questions for the SCENIHR mandate. As such the background cannot be changed by the SCENIHR. No action needed.

			the safety of nanomedicine in this work.	
10	King Mel, Medicines and Healthcare products Regulatory Agency (MHRA), UK, mel.king@mhra.gsi.gov.uk, United Kingdom	1. BACKGROUND	Page 7 gives an overview list of, I gather, notifications in relation to nanomaterials to CAs. This looks to me as a clinician rather narrow and holds a specific speciality focus. This somewhat misleads the reader in terms of the clinical impact of nanotechnologies. The list on p19/20 is much more balanced and provides broader perspective but the implication is that some of these important clinical areas have not been formally shared with CAs. Is this true or is the written narrative unclear?	The background is text provided by the European Commission formulating the questions for the SCENIHR mandate. As such the background cannot be changed by the SCENIHR. The list of page 19/20 is a more extensive listing of SCENIHR being aware of these scientific developments. No action needed.
11	King mel, MHRA, mel.king@mhra.gsi.gov.uk, United Kingdom	1. BACKGROUND	Page 7 gives an overview list of, I gather, notifications in relation to nanomaterials to CAs. This looks to me as a clinician rather narrow and holds a specific speciality focus. This somewhat misleads the reader in terms of the clinical impact of nanotechnologies. The list on p19/20 is much more balanced and provides broader perspective but the implication is that some of these important clinical areas have not been formally shared with CAs. Is this true or is the written narrative unclear? Page 7 line 18-19 “This type of use has not been clearly attributed to the legislation on medicines or to the legislation on medicinal devices” is stated with regard to intra tumoural injectable iron-	The background is text provided by the European Commission formulating the questions for the SCENIHR mandate. As such the background cannot be changed by the SCENIHR. The SCENIHR Opinion, according to the ToR, is intended as a Guidance how to evaluate the risk when a nanomaterial is used in a medical device. The Opinion is not intended to clarify a borderline issue like the use of iron-oxide nanoparticles. It is for the regulators to decide on such borderline products or more in general on classification issues. No action needed.

			oxide nanoparticles. An opportunity to clarify these borderline issues has been missed in this document. It is unfortunate that the recent EC "Manual on Borderline and Classification in the Community Regulatory Framework for Medical Devices" doesn't refer to any products utilizing nanomaterials (http://ec.europa.eu/health/medical-devices/files/wg_minutes_member_lists/borderline_manual_ol_en.pdf). There are some examples of nano-products classified as Devices in the EU but classified as Medicines in the US. Some clarification on classification would be useful. The following is an example taken from the web-site of Nanobiotix: "NBTXR3, the lead compound of Nanobiotix's NanoXray product pipeline, is a nanoparticle formulation of hafnium oxide crystals for the local treatment of tumors to enhance the efficacy of radiotherapy. NBTXR3 has been classified in the EU as class III medical device and is currently being tested in a European Phase I trial to establish feasibility and safety of NBTXR3 in patients with soft tissue sarcoma. Preliminary data are expected by the end of 2012. Further clinical trials are in preparation in Europe and in the US, where NBTXR3 is classified as a drug." http://www.fiercebiotech.com/press-releases/pharmaengine-and-nanobiotix-sign-	

			asia-pacific-exclusive-license-and-collabo. As there may be potential risks to public health, if inappropriate regulatory pathways are followed, the provision of Guidance on the correct classification of nano-based products as either Medicinal Products or Medical Devices would therefore be in the interests of public health.	
12	King mel, MHRA, mel.king@mhra.gsi.gov.uk, United Kingdom	1. BACKGROUND	Page 7 Page 7 gives an overview list of, I gather, notifications in relation to nanomaterials to CAs. This looks to me as a clinician rather narrow and holds a specific speciality focus. This somewhat misleads the reader in terms of the clinical impact of nanotechnologies. The list on p19/20 is much more balanced and provides broader perspective but the implication is that some of these important clinical areas have not been formally shared with CAs. Is this true or is the written narrative unclear? Page 7 line 18-19 “This type of use has not been clearly attributed to the legislation on medicines or to the legislation on medicinal devices” is stated with regard to intra tumoural injectable iron-oxide nanoparticles. An opportunity to clarify these borderline issues has been missed in this document. It is unfortunate that the recent EC “Manual on Borderline and Classification in the	The background is text provided by the European Commission formulating the questions for the SCENIHR mandate. As such the background cannot be changed by the SCENIHR. The SCENIHR Opinion, according to the ToR, is intended as a Guidance how to evaluate the risk when a nanomaterial is used in a medical device. The Opinion is not intended to clarify a borderline issue like the use of iron-oxide nanoparticles. It is for the regulators to decide on such borderline products or more in general on classification issues. No action needed.

			Community Regulatory Framework for Medical Devices" doesn't refer to any products utilizing nanomaterials (http://ec.europa.eu/health/medical-devices/files/wg_minutes_member_lists/borderline_manual_ol_en.pdf). There are some examples of nano-products classified as Devices in the EU but classified as Medicines in the US. Some clarification on classification would be useful. The following is an example taken from the web-site of Nanobiotix: "NBTXR3, the lead compound of Nanobiotix's NanoXray product pipeline, is a nanoparticle formulation of hafnium oxide crystals for the local treatment of tumors to enhance the efficacy of radiotherapy. NBTXR3 has been classified in the EU as class III medical device and is currently being tested in a European Phase I trial to establish feasibility and safety of NBTXR3 in patients with soft tissue sarcoma. Preliminary data are expected by the end of 2012. Further clinical trials are in preparation in Europe and in the US, where NBTXR3 is classified as a drug." http://www.fiercebiotech.com/press-releases/pharmaengine-and-nanobiotix-sign-asia-pacific-exclusive-license-and-collabo As there may be potential risks to public health, if inappropriate regulatory pathways are followed, the provision of Guidance on the correct classification of nano-based	

			products as either Medicinal Products or Medical Devices would therefore be in the interests of public health.	
13	king mel, MHRA, mel.king@mhra.gsi.gov.uk, United Kingdom	1. BACKGROUND	Page 7 line 26 -28 With regard to risk assessment and the "decentralised regulatory system ("New Approach")". It is understood that there is no central data base where details of Devices are kept. With regard to nanomaterials the lack of record keeping and transparency seems incongruous with other EU measures to control nanomaterials. It is understood that the EC has conducted a consultation on a nano-registry as part of REACH legislation http://ec.europa.eu/enterprise/sectors/chemicals/reach/nanomaterials/index_en.htm .It seems incongruous to have a registry for nanomaterials used in industrial applications such as construction or electronics but not keep a registry of nanomaterials when direct human exposure is more likely as is the case for invasive medical devices. It is considered important in this evolving area that there is a registry and transparency as to the nature and extent of data on these nano-device products. Page 7 line 40 The statement, "Special care shall be applied when devices contain or consist of nanomaterial that can be released into the patient's body. The risk	The background is text provided by the European Commission formulating the questions for the SCENIHR mandate. As such the background cannot be changed by the SCENIHR. Page 7 line 26 -28. This is not a topic within the mandate of SCENIHR. Decisions for a registry should be taken by policy makers or regulators. Page 7 line 40. This is not a topic within the mandate of SCENIHR. This should be decided by regulators. Please note that these texts are quotes from the proposal. As you may be aware, the proposal is still under discussion in Council WG and in the European Parliament. No action needed.

			classification influences the stringency of the applicable conformity assessment procedure" could be strengthened. It is noted that new draft Devices regulations states "(13) There is scientific uncertainty about the risks and benefits of nanomaterials used for medical devices…..necessary to introduce a uniform definition for nanomaterials in the design and manufacture of medical devices, the manufacturers should take special care when using nanoparticles that can be released to the human body and those devices should be subject to the most severe conformity assessment procedure. (Reference: 2012/0266 (COD) Proposal for a regulation…on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (http://ec.europa.eu/health/medical-devices/files/revision_docs/proposal_2012_542_en.pdf)) It is further noted that in the Preliminary Opinion the following stated: "The proposal designates medical devices containing nanomaterials in the highest risk class (class III), because of the uncertainties still associated with the potential risks of nanomaterials" (Page 10 line 33 -35). As these products are high risk it is suggested that consultation with the Competent Authority should always, amending the	

			sentence as follows: “Special care shall be applied when devices contain or consist of nanomaterial that can be released into the patient’s body. The risk classification influences the stringency of the applicable conformity assessment procedure”. It is recommended that such Devices should be classified as Class III and that consultation with Competent Authorities should be undertaken.	
14	King Mel, Medicines and Healthcare products Regulatory Agency (MHRA), UK, mel.king@mhra.gsi.gov.uk, United Kingdom	1. BACKGROUND	Page 7 gives an overview list of, I gather, notifications in relation to nanomaterials to CAs. This looks to me as a clinician rather narrow and holds a specific speciality focus. This somewhat misleads the reader in terms of the clinical impact of nanotechnologies. The list on p19/20 is much more balanced and provides broader perspective but the implication is that some of these important clinical areas have not been formally shared with CAs. Is this true or is the written narrative unclear?	The background is text provided by the European Commission formulating the questions for the SCENIHR mandate. As such the background cannot be changed by the SCENIHR. No action needed
20	Dahms Janell, 3M/3M ESPE Dental Producs Division, jkdahms@mmm.com, United States	1. BACKGROUND	Lines 37-40 “In addition, the general safety and performance requirements now contain a specific requirement to design and manufacture medical devices in such a way as to reduce to a minimum the risks linked to the size and the properties of particles used.” This statement and others throughout the SCENIHR document seem to imply that all	The background is text provided by the European Commission formulating the questions for the SCENIHR mandate. As such the background cannot be changed by the SCENIHR. Please note that these texts are quotes from the proposal. As you may be aware, the proposal is still under discussion in Council WG and in the European

			particles present in medical devices pose health risks which need to be reduced. However, this is not the case for particles with low inherent toxicity or where release of particles from the device is not toxicologically significant. We suggest changing ". . . reduce to a minimum the risks linked . . ." to ". . .reduce to a minimum any risks linked . . . ." This would help to clarify that (nano)particles in medical devices do not necessarily pose a health risk. As is stated later in the document, the potential health risks of nanomaterials used in medical devices need to be evaluated on a case-by-case basis.	Parliament. No action needed.
21	Stock Gregor, FIDE - Federation of the European Dental Industry, g.stock@fide-online.org, Germany	1. BACKGROUND	Line 12 and 13 mentions some types of dental materials; however, there are much more dental materials containing nanomaterials according to the EU definition. In our Opinion instead of the two lines one line "many dental materials for filling, luting, impression and other purposes" would be more reliable.	The background is text provided by the European Commission formulating the questions for the SCENIHR mandate. As such the background cannot be changed by the SCENIHR. No action needed.
22	FLAMENT Guillaume, Nanotechnology Industries Association (NIA), guillaume.flament @nanotechia.org,	1. BACKGROUND	This Guidance should take note that the Medical Devices Regulation recast [1] has not been published and nano-specific provisions are not fixed. In this regard, the European Parliament's amended version significantly changes the scope of the regulation regarding nanomaterials as only	The background is text provided by the European Commission formulating the questions for the SCENIHR mandate. As such the background cannot be changed by the SCENIHR. No action needed.

	Belgium		devices where the nanomaterial is intended to be released are concerned by Rule 19 [2]: Amendment 304 'All devices incorporating or consisting of nanomaterial deliberately intended to be released into the human body are in class III.' [1] Proposal 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 [2] European Parliament legislative resolution of 2 April 2014 on the proposal 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)0542 – C7-0318/2012 – 2012/0266(COD)) (Ordinary legislative procedure: first reading)	
23	king mel, MHRA, mel.king@mhra.gsi.gov.uk, United Kingdom	2. TERMS OF REFERENCE	1. TERMS OF REFERENCE Page 8 line 9- 15 If examples of devices are to be given then examples of both invasive and non-invasive devices should be given. Currently only examples of invasive devices are to be given. Page 8 line 12 "Wound care materials" would be better stated as "Dressings for wound care", Dressings are often considered Devices. Other wound care materials might be considered Medicinal Products; for	The terms of reference is text provided by the European Commission formulating the questions for the SCENIHR mandate. As such the terms of reference cannot be changed by the SCENIHR. No action needed.

			example products to treat wounds and infection such as anti-septics and desloughing agents are considered medicinal products.	
24	king mel, MHRA, mel.king@mhra.gsi.gov.uk, United Kingdom	2. TERMS OF REFERENCE	Page 8 Line 15 “Injectable Nanomaterials” should be amended to “injectable nanomaterials (in certain very rare cases)” if indeed the example of injection is required at all. By stating “injectable nanomaterial” (without further qualification) as an example of an invasive device, the impression is given that classification of injectable nanomaterials as Devices is a common occurrence. This is misleading as the majority of injectable nanomaterials are classified as medicinal products not medical devices. Although, the document makes reference to one injectable nanomaterial containing product classified as a Device (reference to Magforce’s NanoTherm is made on pages 7 and 19 and there may be another injectable nano-device product approved for marketing i.e. Sienna+ from Endomagnetics http://www.endomagnetics.com/?page_id=895), these products are in the minority compared to the many injectable Medical Products containing nanomaterials already marketed in the EU. The following list gives examples of injectable nanopharmaceuticals classified as Medicinal Products rather than	The terms of reference is text provided by the European Commission formulating the questions for the SCENIHR mandate. As such the terms of reference cannot be changed by the SCENIHR. No action needed.

			Devices (details may be found on the MHRA* or EMA**web-sites concerning authorisation of these medicinal products): Liposomal amphotericin B (an antifungal) for injection or infusion: • Ambisome (PL16807/0001) Authorised 11/09/1998 • Abelcet (PL 14776/0110) Authorised 16/02/2006 • Abelcet (PL 16260/0015) Authorised 16/02/2006 LiposomalDoxorubicin • Caelyx (Doxorubicin) ((EMA licence) EU/1/96/011/001-004) Authorised 21/06/1996 • Myocet (Doxorubicin) (EMA licence) EU/1/00/141/001-002) Authorised 13/07/2000 Liposomal Daunorubicin • Daunoxome (Daunorubicin) PL 27927/0007 Authorised 03/07/2006 Liposomal Cytarabine • Depocyt (cytarabine) (EMA licence) EU/1/01/187/001) Authorised 11 July 2001 Liposomal Morphine • Depodur PL 13621/0040 Authorised 20/04/2006 Liposomal/Lipidic Verteporfin • Visudyne (EMA licence) EU/1/00/140/001 (Liposome/Lipidic verteporfin) Authorised 1127/07/2000 Albumin bound paclitaxel	

			• Abraxane (EMA licence) EU/1/07/428/001-002) Authorised 11/01/2008 Albumin based radiopharmaceutical diagnostic agents • Nanocoll PL 16991/0001 Authorised 15 June 1998 • Nanotop PL 41222/0002 Authorised February 2014 The following parenteral iron products are nano-colloids: • Venofer , Iron Sucrose PL 15240/0001 Authorised 1998 • Cosmofer, Iron Dextran PL 18328/0001 (DK/H/169/1) Authorised 2001 • Ferinject, Ferric Carboxymaltose UK/H/894/0001/DC PL 15240/0002 Authorised 2007 • Monofer, Iron dextran 1000 complex SE/H/734/01/DC PL 18380/0001 Authorised 2010 • Rienso, Ferumoxytol (EMA licence) EMEA/H/C/002215 Authorised 2012 *MHRA web-site (Medicines Information: SPC & PIL): http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs/index.htm **EMA web-site – (Find a medicine): http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124	

25	king mel, MHRA, mel.king@mhra.gsi.gov.uk, United Kingdom	2. TERMS OF REFERENCE	Page 10 line 33 -35 It is stated with regard to the new Devices Directive that "The proposal designates medical devices containing nanomaterials in the highest risk class (class III), because of the uncertainties still associated with the potential risks of nanomaterials". It is agreed that there are uncertainties with regard to risk. There is an issue of transparency in decision making. One difference in the regulation of Medicinal Products compared to Medical Devices is that with Medicines there is transparency. All Competent Authorities can see the data supporting an application. With Devices this transparency is absent. Furthermore there is transparency with regard to the public as Public Assessment Reports are published for medicines – they are not published for Devices. This further increases the need for clarity on whether some of these nano-based products should not more appropriately be classified as Medicines rather than Devices. For example: The MagForce brain tumour product was approved by a Notified Body in DE for pan-European marketing, Competent Authorities in DE and other member states had no say in its approval or sight of the data supporting its use. Is this appropriate when there are "uncertainties still associated with the use of nanomaterials"? This following is stated on the company web-site with regard to its approval by a notified	The terms of reference is text provided by the European Commission formulating the questions for the SCENIHR mandate. As such the terms of reference cannot be changed by the SCENIHR. In addition: This is not a topic within the mandate of SCENIHR. This should be decided by regulators. Please note that these texts are quotes from the proposal. As you may be aware, the proposal is still under discussion in Council WG and in the European Parliament. No action needed.

			body: “28.06.2010 MagForce Nanotechnologies AG receives European regulatory approval for its Nano Cancer® therapy Berlin - Following two decades of intensive research and development efforts, MagForce Nanotechnologies AG, a Berlin-based medical technology company founded in 1997, has received European regulatory approval for its Nano-Cancer® therapy. The official notice of regulatory approval signifies that the authorized testing centers in Germany responsible for conformity evaluation of medical devices have completed their examination of the application submitted for market approval of Nano-Cancer® therapy and that the approved medical devices fulfill all requirements with regard to quality, safety and medical efficacy. The regulatory approval covers the treatment of brain tumors throughout the European Union”. http://www.magforce.de/en/presse-investoren/news-events/detail/article/magforce-nanotechnologies-ag-erhaelt-europaeische-zulassung-fuer-die-nano-krebsR-therapie.html	
26	king mel, MHRA, mel.king@mhra.gsi.gov.uk, United	2. TERMS OF REFERENCE	Page 11 Just noting the broader topics not addressed. These are likely to grow and substantially in the short to mid-term future – are these areas excluded or will they be	The areas mentioned on page 11 were excluded as they are less likely to result in exposure or are regulated by other regulations (e.g. contrast agents). The issue of borderline products was not

	Kingdom		considered in due course? Page 12 Line 17-19 It is stated that “In addition, by analogy, parts of this Guidance may also be useful for the evaluation of nanomaterials when used in medicinal products including tissue engineered medical products”. Medicinal Products are mentioned but the opportunity to clarify borderline issues has not been taken (see also Page 7 line 18-19 “This type of use has not been clearly attributed to the legislation on medicines or to the legislation on medicinal devices”).	part of the mandate of SCENIHR as described in (1) Background and (2) Terms of Reference. Clarification should be given by regulators. No action needed.
27	Berzanskis Laurel , Health Care Without Harm Europe , laurel.berzanskis@hcwh.org, Belgium	3.1. Introduction	Lines 28-30 - This definition of persons who may be affected is too limited. It is entirely feasible that carers, family members, friends and workers other than healthcare professionals may come in contact with nanomaterials in medical devices either in a healthcare setting or in the home. Exposure can occur in a variety of situations, such as disposal of excreta from patients, handling of nanomaterial contaminated items and spillages, consumption of food and beverages that have come into contact with nanoscale devices, and cleaning and maintenance of areas where nanoscale devices are handled. The Guidance should include all persons who can come into contact with the medical device containing nano materials. Attached: Mahapatra, I. et al. Potential environmental implications of	SCENIHR has limited the application of the Guidance to users (health care professionals) and patients as these are considered potentially high risk groups for exposure via medical devices. SCENIHR does not perform any risk assessment excluding exposure scenarios. Issues referring to the health care professionals can also be used for any other individual taking care of a patient and consequently coming into contact with nanomaterials in medical devices. This has been specified in the final Opinion. The Guidance is limited to the use of nanomaterials in medical devices itself and how to perform a risk assessment of such devices when nanomaterials are used in the production of the devices. Other risks (e.g. occupational, environmental) are excluded.

			nano-enabled medical applications: critical review. Environmental Science: Processes & Impacts 15, 123-144 (2013). Murashov, V. Occupational exposure to nanomedical applications. WIREs Nanomedicine and Nanobiotechnology 1, 203-213 (2009). EU-OSHA. E-fact 73: Nanomaterials in the healthcare sector: occupational risks and prevention (2013).	
28	Berzanskis Laurel , Health Care Without Harm Europe, laurel.berzanskis@hcwh.org, Belgium	3.1. Introduction	Lines 41-43 - It is unreasonable for the Guidance document to have excluded the disposal of medical devices containing nanomaterials, as this is not only an important aspect of hospital practice, but may also occur accidentally.	SCENIHR agrees this is an important aspect, that involve also environmental issues, but it was not included in the ToR. In view of the questions asked by the European Commission SCENIHR had to limit the scope of the Guidance.
29	king mel, MHRA, mel.king@mhra.gsi.gov.uk, United Kingdom	3.1. Introduction	3.1 Introduction Page 10 line 10 It is stated that "This Guidance focuses specifically on medical devices". Perhaps one of the first issues that should be addressed is whether the product is a Medicinal Product or Medical Device. Perhaps it should be stated that consultation with Competent Authorities should occur with regard to classification should be undertaken in all but the most straight-forward cases. Page 10 line 10 Although the Preliminary Opinion focuses on	In order to explain the focus of the Opinion the definition of a medical device as present in the Medical Device Directive (93/42/EEC and additions) is included in the Opinion. For the possible use of combination devices the following text was added on page 10 to explain the regulation/evaluation of such products. "It is noteworthy that where devices incorporate as an integral part a substance, which if used separately, may be considered to be a medicinal product then the safety, quality and usefulness of

			the Medical Device Directive, the Guidance should also note that where devices incorporate as an integral part, a substance, which if used separately, may be considered to be a medicinal product then the safety, quality and usefulness of the medicinal substance must be verified by analogy with the methods required by in Directive 2001/83/EC (Medicinal Products for Human Use) concerning the testing of medicinal products. In practice, such products are regarded as Class III, high risk devices and a consultation is carried out by the Notified Body with a Medicines Competent Authority. This is particularly relevant for nanomaterial containing devices which may on occasion be considered combination products. In the Guidance , this could be addressed by amending to 'This Guidance focuses specifically on medical devices, including those incorporating nanomaterial ancillary medicinal substances". Further explanation of Class III under Rule 13 of the Medical Device Directive might also be provided.	the medicinal substance must be verified by analogy with the methods required by in Directive 2001/83/EC (Medicinal Products for Human Use) concerning the testing of medicinal products. "
30	king mel, MHRA, mel.king@mhra.gsi.gov.uk, United Kingdom	3.1. Introduction	Page 11 line 38 -40 It is stated that "While medical imaging equipment is classified as medical devices, contrast agents, which may include or consist of nanomaterials, are medicinal products". MHRA would agree with the EC on this statement. That said some inconsistencies appear to have arisen in	SCENIHR agrees with the comment. However, the registration of similar products via two different regulations is an issue that is not part of the SCENIHR mandate, and should be decided upon by regulators.

			Europe on this issue. Similar products appear to have been classified differently as either Medicine or Product. Example: Currently marketed are two radiopharmaceuticals which are nano-colloidal, human albumin based products which are injectable diagnostic agents and classified as Medicinal Products. These medical products are for imaging sentinel nodes. Also marketed is Sienna+ is a Class IIa Device which appears to be an injectable formulation of paramagnetic iron oxide nanoparticles which may also be used for sentinel node imaging but using MRI. Thus, both of these nano-based diagnostic agents are used for sentinel node imaging and yet one is classified as Medicine and the other a Device. Given the similarities in the products some inconsistency in the European way of regulating diagnostic agents is demonstrated by this example. (It is noted that Nanocoll/Nanotop are radiopharmaceuticals specifically mentioned in the Medicinal Products for Human Use Directive (2001/83/EC)). Details of the Medicinal Products Nanocoll and Nanotop may be found on the MHRA web-site as follows: Nanocoll PL 16991/0001 Authorised 15 June 1998 http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1386571285623.pdf	No action needed.

			Nanotop PL 41222/0002 (Authorised February 2014) http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs/?prodName=NANOTOP%200.5%20MG%20KIT%20FOR%20RADIOPHARMACEUTICAL%20PREPARATION&subsName=HUMAN%20ALBUMIN&pageID=SecondLevel Details of Sienna+, from Electromagnetics a Class IIa Device may be found at: http://www.endomagnetics.com/?page_id=895	
31	king mel, MHRA, , United Kingdom	3.1. Introduction	Page 11 line 47-51 Page 12 line 1-4 Definitions are important in understanding whether a particular product falls within the scope of the Preliminary Opinion. As there is still some debate regarding the definition nanomaterial the Preliminary Opinion should acknowledge that the definition might change and that care is needed in its interpretation. Although the definition given in the Preliminary Opinion is as stated in the proposed (not final) Devices Directive* it should be noted that this definition has a caveat to allow amendment in view of scientific progress as follows: "The Commission shall be empowered to adopt delegated acts in accordance with Article 89 in order to adapt the definition of nanomaterial set out in number (15) of	SCENIHR agrees with the comment and additional text is included on page 12. "It should be noted that in the Commission Recommendation for a nanomaterial (EC 2011) the possibility for a review and adaptation of the definition is included in view of technical and scientific progress and taking into account definitions agreed at Union and international level."

			paragraph 1 in view of technical and scientific progress and taking into account definitions agreed at Union and international level." (*see 2012/0266 (COD) Proposal for a regulation…on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (http://ec.europa.eu/health/medical-devices/files/revision_docs/proposal_2012_542_en.pdf) With regard to the EC definition of nanomaterial, there still appears to be debate. March 2014 saw the publication of the European Commission JCR report "Towards a review of a definition of the term "nanomaterial". The definition is not finalised in this document. Furthermore, the EC has previously noted that "(17) Given the special circumstances prevailing in the pharmaceutical sector and the specialised nano-structured systems already in use, the definition in this Recommendation should not prejudice the use of the term 'nano' when defining certain pharmaceuticals and medical devices," Commission Recommendation of 18 October 2011on the definition of nanomaterial http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:275:0038:0040:EN:PDF	

			Therefore it is suggested that the Preliminary Opinion states (page 11 line 47-48) includes the following extra sentence: The Guidance addresses the use of nanomaterials as defined in the recommendation of the European Commission of October 2011 (Commission Recommendation 2011/696/EU) 48 (EC 2011), which is also used in the proposed regulation on Medical Devices. However, as there is continuing debate on the definition nanomaterial care should be taken not to exclude materials falling just outside the proposed definition. Where a product might possibly be a nanomaterial or borderline nanomaterial manufacturers should consult with competent authorities. It should also be noted that current definitions might be amended.	
32	Dahms Janell, 3M/3M ESPE Dental Products Diviion, jkdahms@mmm.com, United States	3.1. Introduction	Lines 38-39 "...free nanomaterials in a paste-like formulation (e.g. dental filling composites),..." Composite products will be cured (polymerized) in their final form, resulting in a device where nanomaterials are in an embedded or bound format; any potential patient or practitioner exposure to free nanomaterials will be extremely brief or nonexistent based on the physical (e.g., paste) form of the product. This should be	Lines 39 – 39: SCENIHR agrees with the comment. This aspect is discussed in the risk assessment of dental materials in section 3.5.1. In the Abstract and Introduction just a general indication is presented of the types on medical devices that contain nanomaterials. Indeed the assessment of a low likelihood of exposure to free nanoparticles due to polymerization is part of the risk assessment.

			clarified.	
33	Schmidt Cathrine, Bayer HealthCare, cathrine.schmidt@bayer.com, Germany	3.1. Introduction	Comment on the scope of the preliminary Opinion: In page 12, it is stated: "Although this Guidance specifically addresses the use of nanomaterials in medical devices and the generation of nano-sized wear and tear particles, this Guidance may also be applicable for the evaluation of medical devices containing or generating particles, which are not covered by the above definition of nanomaterial". It would be beneficial to have examples of what is not under the nanomaterial definition but still to be considered in the scope of the Opinion.	SCENIHR intended to indicate that the Guidance may also be useful for the evaluation of particles that are larger than 100 nm, which as such are not covered by the definition of a nanomaterial.
34	Stock Gregor, FIDE - Federation of the European Dental Industry, g.stock@fide-online.org, Germany	3.1. Introduction	a.) The fact that nanomaterials are relatively free moving in a liquid or paste, like in a dental composite before polymerization, does not mean that nanoparticles are readily available at the surface of those medical devices. As long as wettability of nanoparticles by the liquid phase exists they are covered by a liquid film (Heumann et al. I, 1979). Capillary forces (Heumann et al. II, 1979) keep them inside the liquid or paste. In order to expose them to the surface it is necessary that a reaction takes place that destroys wettability or a pressure is applied that exceeds capillary forces. Nanoparticles may also move when the liquid or paste is	SCENIHR agrees with the comment. The presence of free nanomaterials in paste-like medical devices like dental composites is indicated as an example. It does not indicate any risk category. Whether there is an easy release or not depends on the formulation used and is part of the risk assessment of the medical device.

			mixed with a substance that also shows wettability to the nanoparticles. b.) In line 38-39 dental filling composites are mentioned as examples for “free nanomaterials in a paste like formulation”. In our Opinion this classification is misleading. The dental filling composites are in such a form only for a very short contact time with patients being polymerized immediately after placement and forming a solid body containing the nanoparticles in strongly (chemically) bounded form. Even for pastes the unbound presence of the nanoparticles is not equivalent with an easy release due to the very high viscosity of the pastes.	
35	Sanak Aleksandra, Council of European Dentists (CED), ced@eudental.eu, Belgium	3.1. Introduction	Lines 36 - 44: dental filling materials are listed uner free nanomaterials in paste-like formulations. However, this only is the case for materials in the non-set state. In the mouth they are set and then the nanoparticles are not free anymore. Therefore, this should be adjusted in order to prevent confusion.	SCENIHR agrees with the comment. The presence of free nanomaterials in paste-like medical devices like dental composites is indicated as an example. It does not indicate any risk category. Whether there is an easy release or not depends on the formulation used and is part of the risk assessment of the medical device.
36	FLAMENT Guillaume, Nanotechnology Industries Association (NIA),	3.1. Introduction	Nanoparticles generated from wear-and-tear phenomena in devices where nanomaterials were not used originally should not be covered by this Guidance as the title of the Guidance is directed to ‘nanomaterials used	SCENIHR disagrees with the comment. For fixed coatings and dental materials the release of nanomaterials may primarily occur after wear and tear. However, this may occur for all medical devices, so also wear and tear of medical devices

	guillaume.flament @nanotechia.org, Belgium		in medical devices'.	manufactured without nanomaterials should be considered. No action needed
37	king mel, MHRA, , United Kingdom	3.2. Methodology	3.2. Methodology 3.3. Characterisation of nanomaterials used in medical devices Page 14 lines 17-18 The Preliminary Opinion might also mention that small changes in the characteristics of nanomaterials may greatly affect their properties. This increases the importance of thorough characterisation and control. For example at nano-scale small changes in particle size can significantly affect surface area and reactivity. Page 14 line 19-20 Page 14 line 35-36 Although characterisation at all stages of production is mentioned, the Preliminary Opinion does not seem to differentiate between nanomaterial and nanomaterial integrated with a device. In practice characterisation of the nanomaterial and device usually occurs. The Guidance could make clear this differentiation between nanomaterial and nanomaterial bound or integral to the device. For example the nanosilver wound dressing "Acticoat with Silcryst" is labelled as containing Silcryst nanoocrystals. Characterisation of Silcryst nanocrystals would be expected, however, characterisation when bound to the wound dressing would also be expected. Although it	SCENIHR agrees with the comment. The text on page 12 is adapted and the word "precise" is added. Page 14 Line 35-36. SCENIHR agrees with the comment. The aspect of characterisation of the nanomaterial itself and as it is used is indicated in the Opinion. On p.12, Fig. 1 in the Opinion it is indicated that both nanomaterial per se and nanomaterial in the device should be characterised. Page 14 line 35-36. Although the example is not a medical device, SCENIHR agrees with the comment. Text is added to the Opinion to reflect a possible effect of sterilization on the nanomaterials. In view of these potential surface changes it is important that the physicochemical status of a nanomaterial is determined at different stages of testing and/or usage, (EFSA 2011, SCCS 2012), "including sterilization of the invasive medical devices (Lawrence 1998)."

			is possible that the characteristics of the wound dressing are largely dependent on the Silcryst nanocrystals it might be expected that when bound to the dressing these characteristics are modified. It should perhaps be noted that nanomaterial subsequently released may be modified and as result of integration in a device (although in this case this might not be important depending on degree of shedding, persistence of particles and systemic exposure). The Preliminary Opinion does state "importantly, nanomaterials may change their surface chemistry during processing (Page 14 line 35-36). This could be further stressed to avoid situations where the characterisation and toxicology are performed on material before further processing into the finished product. Page 14 line 35-36 Many of the invasive medical devices are sterile. Sterilization methods such as moist or dry heat can affect nanomaterials. Although the effect of sterilization on a device is normally considered, the Guidance could make it clear that this is expected. There are historical reports that the sterilization process affects the stability of iron nanoparticles (Iron Dextran). In 1991 supply of Iron Dextran to the US market was disrupted as a consequence of regulatory action by the FDA. It appeared that changes in the sterilization	

			heating step affected the binding of the dextran complex/coating to the particle with resultant stability issues (see Knapp, CJ, Schien Pharmaceuticals InFedTM reopened IV iron market for dialysis patients Nephrology News and Issues 10, (June 1992) This incident is further discussed by Lawrence R. (1998) PDA journal of pharmaceutical Science and Technology pp 190-197 which states; “since the sterilization technique appears to have caused some of the manufacturing problems that resulted in first discontinuance of lot releases and then subsequent market withdrawal of IDref, process alterations in production of iron dextran complex became necessary”. As sterilization processes can alter nanomaterials it is perhaps necessary to consider the characteristics of the nanomaterial after sterilization. It should perhaps be noted that nanomaterial subsequently released may be modified and as result of the sterilization process. This should be considered by Device manufacturers. It is possible that they may be able to demonstrate that the nanomaterials in question are not altered by the sterilization process or manufacturing processes employed.	
38	king mel, mhra, ,	3.2.	Page 14 lines 21-22 The Preliminary Opinion should state that manufacturing process may	Page 14 lines 21-22

	United Kingdom	Methodology	characterise a nanomaterial. Some nanomaterials can defy full characterisation. In these cases adherence to well defined manufacturing processes may be necessary to characterise them or at least fix their characteristics. In chemically complex medicinal products, which defy full characterisation, these principles of control by process are applied. For example EMA Guidance on biological molecules states: "As for any biological medicinal product, the biosimilar medicinal product is defined by the molecular composition of the active substance resulting from its manufacturing process, which may introduce its own molecular variants, isoforms or other product-related substances as well as process-related impurities".(EMA/325027/2013 Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/06/WC500167838.pdf . The importance of manufacturing process, as a means to ensure nanomaterial characteristics, is also mentioned in, EMA Reflection Papers on Nanopharmaceuticals. For example, in the guideline on surface coatings for parenteral nanomaterials the following is stated: "Control and assurance of the quality of	These are relevant comments in principle, however , so far there are no indications that nanomaterials can be characterised by their production technique. As such, nanomaterials always have a size distribution, so it is never a homogeneous material. In addition, Fig.1 includes possibilities for re-evaluation.

			coated nanomedicine products cannot just be based upon a set of test specifications on the final product. It requires a well-defined and controlled manufacturing process supplemented with a suitable control strategy (appropriate in process controls for the critical steps of the manufacture of the product including the coating process). (EMA/325027/2013 Reflection paper on surface coatings: general issues for consideration regarding parenteral administration of coated nanomedicine products http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/08/WC500147874.pdf). Page 14 lines 21-22 The Guidance should perhaps consider where re-evaluation of the characteristics and risks of nanomaterials should be undertaken. Although, it is already a requirement for devices that re-evaluation of risk should occur when significant processing changes occur, the Guidance could emphasis this requirement for nanomaterials. An EMA reflection paper on data requirements for nanopharmaceutical liposomal products states: “Comparative investigations (see Quality Characterisation section) should be undertaken when a change is introduced into the manufacturing process during development but also after marketing authorisation (e.g. for scale up).	

			(EMA/CHMP/806058/2009/Rev. 02, Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product,http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/03/WC500140351.pdf	
39	Berzanskis Laurel, Health Care Without Harm Europe, laurel.berzanskis@hcwh.org, Belgium	3.3. Characterisation of nanomaterials used in medical devices	Page14, line 17-18 - Properties of nanomaterials that influence toxicity include: chemical composition, surface charge, catalytic behaviour, extent of particle aggregation or disaggregation, and the presence or absence of other groups of chemicals attached to the nanomaterial. The greater chemical reactivity and bioavailability of nanomaterials may also result in greater toxicity of nanoparticles compared to the same unit of mass of larger particles. Attached articles for this comment: Hoet P, Bruske-Holfeld I, Salata O. Nanoparticles – known and unknown health risks. Journal of Nanobiotechnology. 2004;2:12. Sayes CM, Fortner JD, Guo W, Lyon D, Boyd AM, Ausman KD, et al. The differential cytotoxicity of water-soluble fullerenes. . Nano Letters. 2004;4(10):1881-7. Brunner T, Piusmanser P, Spohn P, Grass R, Limbach L, Bruinink A, et al. In Vitro Cytotoxicity of Oxide Nanoparticles: Comparison to Asbestos, Silica, and the	Page14, line 17-18 SCENIHR does not disagree with the comment. However, chapter 3.3 deals with the characterisation of the nanomaterial. Toxicity and/or potential risk is not an issue in this chapter. The chapter 3.7 on Toxicological evaluation section 3.7.1 Introduction considers these toxicity aspects on page 29. Line 32-33 reads: “The toxicity of nanomaterials is a response to the size and additional specific characteristics, most of them listed in Table 1. “ Regarding references – Various references are already included in the Preliminary Opinion (publications 2011-2014). Page 14, line 29-32. SCENIHR agrees with the comment. The text on page 14 line 29-32 specifically asks for the information as mentioned in the comment. This section draws the attention to the fact that a

			Effect of Particle Solubility.Enviromental Science Technolology. 2006;40:4374-81. Magrez A, Kasa S, Salicio V, Pasquier N, Won SJ, Celio M, et al. Cellular toxicity of carbon-based nanomaterials. Nano Letters. 2006;6(6):1121-5. Sayes C, Wahi R, Kurian P, Liu Y, West J, Ausman K, et al. Correlating nanoscale titania structure with toxicity: A cytotoxicity and inflammatory response study with human dermal fibroblasts and human lung epithelial cells. Toxicological Science. 2006;92(1):174-178 Page 14, line 29-32 - It is essential that the kind of justification to be provided is detailed, as it is extremely unlikely that sufficient physicochemical similarity between the nanomaterials exists to consider the data for risk assessment. For instance silver nanoparticle toxicity may also be shape dependent. Pal et al. (2007) speculated that this may be due to the increase in effective surface areas as a result of the different flat areas that together make up the shape of the particle (also known as facet areas), even though the surface area is notionally the same. Different facet types appear to affect the reactivity of the particles. Bacterial inhibition also critically depends on the concentration of nanosilver particles present, as well as initial bacterial numbers. Silver particles may be engineered to have a number of different shapes, including	thorough characterisation is necessary in order to demonstrate that the tox data are related to the nanomaterial present in the medical device, and not based on a different nanomaterial be it with a different shape or size or something else. In addition, the Guidance states on page 17 Line 19-24 that: "No single method was found that could cover the size range from lower than 1 nm to above 100 nm for all materials. This is one of the reasons that both EFSA and SCCS in their Guidance require at least two methods for size determination, one of them being an electron microscopy method (EFSA, 2011; SCCS, 2012). Following this principle, the same is considered to apply to the characterisation of nanomaterials used in medical devices." The reference of Wijnhoven et al., 2009 on nanosilver is already included in the Preliminary Opinion.

			spheres, particles, rods, cubes, wires, film and coatings (Winjhoven et al. 2009). Articles attached for this comment: Pal, S., Y. K. Tak and S. J. Myong (2007). "Does the Antibacterial Activity of Silver Nanoparticles Depend on the Shape of the Nanoparticle? A Study of the Gram-Negative Bacterium Escherichia coli." Applied and Environmental Microbiology 73(6): 1712–1720. Wijnhoven, S. W. P., Peijnenburg, W. J. G. M., Herberts, C. A., Hagens, W. I., Oomen, A. G., Heugens, E. H. W., Roszek, B., Bisschops, J., Gosens, I., M., Dik van de, Dekkers, S., Jong, W. de, Zijverden, M. van, Sips, Adriënne J. A. M. and Geertsma, R. E. (2009). "Nanosilver - a review of available data and knowledge gaps in human and environmental risk assessment". Nanotoxicology (3). First published online 26 March 2009.	
40	Berzanskis Laurel, Health Care Without Harm Europe, laurel.berzanskis@hcwh.org, Belgium	3.3. Characterisation of nanomaterials used in medical devices	Page 14, line 37-40 - Because nanomaterials may acquire new 'biological identities' (i.e. new properties) via the adsorption of biomolecules (the bio-corona) onto their surface, it is furthermore essential during toxicological studies to assess the interaction between these and how these may interact with the physiological response of the organism. Attached article: Fadeel B, Feliu N, Vogt C, Abdelmonem AM, Parak WJ. Bridge over	Page 14, line 37-40. SCENIHR agrees with the comment. Text is added to draw attention to this phenomenon on page 29 in Chapter 3.7.1.

			troubled waters: understanding the synthetic and biological identities of engineered nanomaterials. WIREs Nanomed Nanobiotechnololgy. 2013(5):111-29.	
41	Berzanskis Laurel, Health Care Without Harm Europe, laurel.berzanskis@hcwh.org, Belgium	3.3. Characterisation of nanomaterials used in medical devices	Page 17, table 2 - The table contains a number of empty boxes. In our Opinion they should be filled in. We also query whether the size range should be the only limitation referred to in the table?	SCENIHR agrees with the comment and has completed the table. All boxes are filled in now. The table 2 is an example for the size measurements as its title indicates. The Opinion explains under the table: “More information about various characterization techniques is provided in the Annex.” Performance of some Characterisation Methods
42	Stock Gregor, FIDE - Federation of the European Dental Industry, g.stock@fide-online.org, Germany	3.3. Characterisation of nanomaterials used in medical devices	We doubt that a thorough characterization is always necessary for a proper risk assessment of nanomaterials released from a medical device. Depending on the composition of the medical device only certain information may be necessary.	A proper characterization is also necessary for identification of the nanomaterial. Is the nanomaterial that was used for the tox studies/data the same as the one in the device? If limited characterization is possible justification should be provided. Text has been added to indicate importance of characterisation in relation to identification. Identification is also necessary to show that the nanomaterials on which the toxicological studies were performed, has the same/similar characteristics as the one used in the medical device. If limited characterization is possible justification should be provided.

43	king mel, mhra, , United Kingdom	3.3.1. Physicochemical characterisation of nanomaterials	3.3.1. Physicochemical characterisation of nanomaterials Page 14 lines 33-34 It is stated that “the most important parameters of the nanomaterials intended for use in medical devices are presented in table 1”. The section on physicochemical characterisation of nanomaterials should emphasise the need for validated characterisation of attributes that will affect performance, and that are known to relate to clinical consequence (including safety). The specifications chosen (on a case by case basis) should be justified in relation to proposed use. Furthermore, identification of critical quality attributes is mentioned in the EMA reflection papers on nanopharmaceuticals as follows: • EMA/CHMP/13099/2013 (block copolymer micelles): “It is important to identify the critical quality attributes of block copolymer micelle products that will have a major impact on the in vivo PK and pharmacodynamic (PD) properties that may impact on safety and efficacy. Correctly identifying the parameters that define relevant physicochemical properties of the block copolymer micelle product is critical to ensure its quality”.	The safety evaluation of medical devices is performed according to the harmonised European standard ISO 10993-1 “Biological evaluation of medical devices Part 1 Evaluation and testing within a risk management process. In this evaluation clinical aspects are included such as type of device (e.g. implant), type of tissue contact (e.g. blood), and contact time with the patient (e.g. < 24 hours). For nanomaterials there are yet no validated characterisation methods available. For size, at least two methods need to be considered. The Opinion states on Page 16, Line 17-19: “The most important conclusion is that sizing a particulate material needs to be done using different techniques depending on whether the nanoparticles occur as a powder, are dispersed in a liquid, are coated or are embedded in a solid material.”

			• EMA/CHMP/806058/2009/Rev. 02 (liposomes) “The critical quality attributes of liposomal formulations may have a major impact on the in vivo pharmacokinetic (PK) and pharmacodynamic (PD) properties” • EMA/325027/2013 (surface coating nanomedicines) Consideration of quality, non-clinical and clinical data will play an important role in the definition of the critical product characteristics of a coated nanomedicine. • EMA/CHMP/SWP/620008/2012 (iron nano-colloids) “Correctly identifying the parameters that define relevant physicochemical properties of a nano-sized iron-based colloidal product is critical to ensure its quality”. (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000564.jsp&mid=WC0b01ac05806403e0) Page15 line 3 (Table 1 row stating “Chemical Composition/ Identity”) Control of starting materials can also be essential in characterising or ensuring the characteristics of nanoparticles. Although Table 1 states that the “chemical composition of the coatings (and) constituents of nanomaterials must be provided”, the Guidance could	Page 15, Line 3 (Table 1 row stating “Chemical Composition/ Identity”). Page 14. Line 26-32 of the Preliminary Opinion clearly states that the nanomaterial itself should be thoroughly characterized. For clarification text is added on Page 14, Lines 26-27.: …used as starting materials for the production of a medical device.

			specifically emphasise the importance of starting materials. The importance of starting materials is highlighted in other regulatory Guidance . For example an EMA reflection paper discusses surfaces coatings on nanoparticles and states “The following are important: Complete characterisation of the coating material, including its composition and control” (EMA/325027/2013 Reflection paper on surface coatings: general issues for consideration regarding parenteral administration of coated nanomedicine productshttp://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/08/WC500147874.pdf). Some nanoparticles may be comprised of polymeric substances. Defining starting materials may be critical in ensuring characteristics. An EMA reflection paper on block copolymer micelle products states “The chemical composition of block copolymers greatly impacts the driving force behind polymer self-association, and therefore, size and physicochemical characteristics and in vitro and in vivo stability of the resultant micelles. Crucial properties include: Chemical structure of the block copolymers…” (EMA/CHMP/13099/2013 Joint MHLW/EMA reflection paper on the development of block copolymer micelle	

			medicinal products http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/01/WC500159411.pdf	
44	king mel, mHRA, , United Kingdom	3.3.2. Methods for characterisation	3.3.2. Methods for characterisation Page 17 Line 10-11 It is agreed that the "characterisation and application of nanomaterials in medical devices is not an easy task". Where nanomaterials are difficult to characterise a range of methods including characterisation of starting materials, manufacturing process, product performance and even toxicokinetic testing may be required. This principle is stated in the Draft EMA reflection paper on iron nanoparticles as follows: "For the comparison of iron-based nano-sized colloidal products developed with reference to an innovator medicinal product, current scientific knowledge and regulatory experience for characterisation of nano-sized colloidal preparations indicate that quality characterisation on its own, would not provide sufficient assurance of the similarity between the two products, even if the quality tests performed show similarity. In the context of such iron based preparations, a "weight of evidence approach" including data from quality, non-clinical and human pharmacokinetic studies is required" (Reflection paper on the data requirements	SCENIHR agrees with the comment. The text on page 17 Line 10-11 was adapted. "Where nanomaterials are difficult to characterise a range of methods including characterisation of starting materials, manufacturing process, product performance and even toxicokinetic testing may be used as has been indicated for iron-based nano-sized colloidal medicinal products (EMA 2013)."

			for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product (.EMA/CHMP/SWP/620008/2012) http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500149496&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc)	
45	Berzanskis Laurel, Health Care Without Harm Europe, laurel.berzanskis@hcwh.org, Belgium	3.4. Uses of nanomaterials in medical devices	Page 18, Line 1 - Other diagnostic applications using nanotechnology and already on the market include: colloidal gold particles which, due to their stability, have been widely used to rapidly test for pregnancy, ovulation, HIV and other indications; magnetic nanoparticles used for cell sorting applications in clinical diagnostics; and superparamagnetic iron oxide nanoparticles for magnetic resonance imaging first approved in Europe in 1993. Attached article: Wagner, V. et al. The emerging nanomedicine landscape. Nature Biotechnology 24, 1211-1218 (2006). Page 19, line 13 - We need a comprehensive list of applications under development to understand whether the Guidance is properly addressing potential health effects of nano materials in medical devices.	Page 18, Line 1 SCENIHR agrees with the comment. However, most of the presented examples in the comment are in vitro assays which are not covered in the Guidance . In addition, the examples are not meant to be exhaustive. Page 19, Line 13 As indicated above these listings are not meant to be exhaustive. These are examples for clarification. It is not the intention of SCENIHR to list all medical devices under development. The Opinion cites more recent documents like the proceedings of the European CLINAM & ETPN Summit, June 23-26, 2013 (Löffler 2013). Note that new insights have been gained since the Wagner paper of 2006!
46	king mel, mhra, ,	3.4. Uses of nanomaterials in	3.4. Uses of nanomaterials in medical devices	SCENIHR agrees with the comment. The text has

	United Kingdom	medical devices	Page 19 line 7 The statement "Nanoparticles are additionally being investigated for use in diagnostic imaging (Skotland et al., 2010)." whilst true, this statement seems to suggest that diagnostics is a novel application nanoparticles. In fact there is a long history of 'nanoparticle'-based imaging agents that have come to market globally e.g. Feridex®, Endorem™. GastroMARK®, Lumirem®, Sinerem®, Resovist®, and others. These products are SPIO's (small paramagnetic iron oxide) particles. The majority of these products are classified as Medicines rather than Devices. It is suggested to amend the sentence as follows: "Nanoparticles are additionally being investigated for use in diagnostic imaging (Skotland et al., 2010) and there are several examples in the past of where nanoparticles have been marketed for diagnostic purposes. Historical examples of diagnostic nanoparticles classified as Medicinal Products include the SPIO (small paramagnetic iron oxide) nanoparticles such as Lumirem and Sinerem. Detail of these Medicinal Products may be found on the MHRA (Lumirem) and EMA websites (Sinerem) as follows: MHRA website: Lumirem175 mg/l, oral suspension. (PL 12308 / 0003 Ferumoxsil (siloxane-coated particles of Magnetite)) was authorised 25 October 1994 / 23 March 2005 and is classified as a Medicinal Product for	been adapted on page 19 line 7. "Also for diagnostic imaging nanoparticles have been investigated the last decades (Skotland et al., 2010)."

			"Marking of the gastrointestinal tract in MRI to facilitate the delineation of organs and localisation of lesions". http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1394426182193.pdf EMA website: Sinerem (EMEA/H/C/000801) is a super paramagnetic iron oxide nanoparticle Medicinal Product that was withdrawn before marketing in the EU. It is an MRI contrast agent intended for use in patients with pelvic cancers. Sinerem was considered a Medicinal Product and further details may be found on the EMA web-site as follows: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000801/wapp/Initial_authorisation/human_wapp_000064.jsp&mid=WC0b01ac058001d128	
47	king mel, mhra, , United Kingdom	3.4. Uses of nanomaterials in medical devices	Page 19 line 7 The statement "Nanoparticles are additionally being investigated for use in diagnostic imaging (Skotland et al., 2010)." present in this document might be interpreted that it is routinely acceptable to classify diagnostic nanoparticles as Devices. This is not the case and could lead to difficulties, unless this it is clarified that diagnostic nanoparticles should be classified as Medicinal Products. It is suggested to amend the sentence as follows: "Nanoparticles are additionally being investigated for use in diagnostic imaging	SCENIHR agrees with the comment. The text has been adapted on page 19 line 7. Also for diagnostic imaging, nanoparticles have been investigated the last decades (Skotland et al., 2010). However, diagnostic imaging agents are usually classified as Medicinal Products." That excludes now such an interpretation.

			(Skotland et al., 2010) and there are several examples in the past of where nanoparticles have been marketed for diagnostic purposes. Historical examples of diagnostic nanoparticles classified as Medicinal Products include the SPIO (small paramagnetic iron oxide) nanoparticles such as Lumirem and Sinerem. It is noted that on Page 11 line 38 -40 of this document the following is stated “While medical imaging equipment is classified as medical devices, contrast agents, which may include or consist of nanomaterials, are medicinal products”. This confirms the need to qualify this statement by pointing out that diagnostic imaging agents are usually classified as Medicinal Products. Many nano-based imaging agents are classified as Medicines rather than Devices e.g. Lumirem and Sinerem. Both these products were classified as Medicines rather than devices. Furthermore, many imaging agents not based on nanotechnology are classified as Medicines. MRI and X-ray contrast mediums such as Magnevist (MRI contrast agent) and Xenetrix (X-ray contrast agent) as well as barium sulphate (x-ray contrast medium) are classified as medicinal products Detail of these Medicinal Products may be found on the MHRA (Lumirem) and EMA websites (Sinerem) as follows: MHRA website: Lumirem 175 mg/l, oral	

			suspension. (PL 12308 / 0003 Ferumoxsil (siloxane-coated particles of Magnetite)) was authorised 25 October 1994 / 23 March 2005 and is Classified as a Medicinal Product for "Marking of the gastrointestinal tract in MRI to facilitate the delineation of organs and localisation of lesions". http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1394426182193.pdf EMA website: Sinerem (EMEA/H/C/000801) is a super paramagnetic iron oxide nanoparticle Medicinal Product that was withdrawn before marketing in the EU. It is an MRI contrast agent intended for use in patients with pelvic cancers. Sinerem was considered a Medicinal Product and further details may be found on the EMA web-site as follows: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000801/wapp/Initial_authorisation/human_wapp_000064.jsp&mid=WC0b01ac058001d128 Furthermore details of the examples Magnevist, Xenetrix as well as Barium sulphate may be found on the MHRA web-site as follows: Xenetrix is solution for injection used as an intravenous X-ray contrast medium. http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs/?prodNam	

			e=XENETIX%20300%20(300%20MGI/ML)%20SOLUTION%20FOR%20INJECTION)&subsName=IOBITRIDOL&pageID=SecondLevel Magnevist® is a solution for injection for MRI imaging: http://www.mhra.gov.uk/Safetyinformation/%20Medicinesinformation/SPCandPILs/index.htm?prodName=MAGNEVIST%202MMOL/%20L%20SOLUTION%20FOR%20INJECTION&subsName=GADOPENTETIC%20ACID%20DIMEGLUMINE%20SALT&pageID=SecondLevel Barium sulfate is an X-ray contrast medium classified as a medicine. For examples , (E-Z-HD 98% powder for oral suspension and Polibar 94% powder for rectal suspension) see MHRA website as follows: http://www.mhra.gov.uk/Safetyinformation/%20Medicinesinformation/SPCandPILs/index.htm?subsName=BARIUM%20SULFATE&pageID=SecondLevel	
48	king mel, mhra, , United Kingdom	3.4. Uses of nanomaterials in medical devices	Page 20 line 4 The definition of a Medicinal product is as follows: Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to	Page 20 line 4. SCENIHR agrees with the comment. For clarification the proposed text has been included. “Theranostics (therapy combined with diagnostics), i.e. combination of diagnostics and heat therapy with the aid of super paramagnetic iron oxide nanoparticles (as this type of product is still under development, this type of use has not been clearly attributed to the legislation on medicines or to the

			making a medical diagnosis. (Article 1 Directive 2001/83/EC as amended by Directive 2004/27/EC) Mention of "Theranostics (therapy combined with diagnostics)" in this document on Devices may give the erroneous impression that such agents may automatically be considered Devices. Even when considering diagnostics (without therapy) there are clear legal reasons why they may be considered Medicinal Products (see above definition). Furthermore there are many examples of nano-nased diagnostic contrast agents that are classified as medicinal products e.g. Lumirem and Sinerem. Indeed the Preliminary Opinion recognises that "While medical imaging equipment is classified as medical devices, contrast agents, which may include or consist of nanomaterials, are medicinal products" (Page 11 line 38 -40) It is suggested that the following is stated: "Theranostics (therapy combined with diagnostics), i.e. combination of diagnostics and heat therapy with the aid of super paramagnetic iron oxide nanoparticles (as this type of product is still under development, this type of use has not been clearly attributed to the legislation on medicines or to the legislation on medicinal devices, however, it is likely that these products may be considered Medicinal	legislation on medicinal devices, however, it is likely that these products may be considered Medicinal Products)."

			Products)."	
49	Berzanskis Laurel, Health Care Without Harm Europe, laurel.berzanskis@hcwh.org, Belgium	3.5. Exposure to nanomaterials from medical devices	Page 20, line 13-15 - Users is not the appropriate word as healthcare professionals are not the only one who may be exposed – other workers – i.e. cleaners and also visitors/family member or even random passers-by. Exposure can occur in a variety of situations, such as disposal of excreta from patients, handling of nanomaterial contaminated items and spillages, consumption of food and beverages that have come into contact with nanoscale devices, and cleaning and maintenance of areas where nanoscale devices are handled. The Guidance should include all persons who can come into contact with the medical device containing nanomaterials. Mahapatra, I. et al. Potential environmental implications of nano-enabled medical applications: critical review. Environmental Science: Processes & Impacts 15, 123-144 (2013). Murashov, V. Occupational exposure to nanomedical applications. WIREs Nanomedicine and Nanobiotechnology 1, 203-213 (2009). EU-OSHA. E-fact 73: Nanomaterials in the healthcare sector: occupational risks and prevention (2013).	SCENIHR has limited the application of the Guidance to users (health care professionals) and patients as these are considered at a potential high risk groups for exposure via medical devices. SCENIHR is indeed not performing any risk assessment excluding exposure scenarios. Issues referring to the health care professionals can also be used for any other individual taking care of a patient and consequently coming into contact with nanomaterials in medical devices. This has been specified in the final Opinion. The Guidance is limited to the use of nanomaterials in medical devices itself and how to perform a risk assessment of such devices when nanomaterials are used in the production of the devices. Other risks (e.g. occupational, environmental) are excluded.
50	Berzanskis Laurel, Health Care	3.5. Exposure to nanomaterials	page 21, lines 37-40 - We suggest that in this case the precautionary principle should	Page 21, lines 37-40.

	Without Harm Europe, laurel.berzanskis@hcwh.org, Belgium	from medical devices	be applied in the case of lack of information. "The precautionary principle enables rapid response in the face of a possible danger to human, animal or plant health, or to protect the environment. In particular, where scientific data do not permit a complete evaluation of the risk, recourse to this principle may, for example, be used to stop distribution or order withdrawal from the market of products likely to be hazardous." Page 24, line 8-9 and table 3 - The potential for broken skin should be considered. Additionally there is no such thing as a non-degradable material.	SCENIHR gives advice on potential risks. Whether the precautionary principle should be applied or not is up to the risk management, and therefore outside of the mandate of SCENIHR. Page 24, line 8-9 and table 3. Broken skin is included in the Table 3 under "Breached or compromised surface". Especially hard plastics and metals can be considered to be non-degradable as they do not disappear during the lifetime of a patient.
51	king mel, mhra, , United Kingdom	3.5. Exposure to nanomaterials from medical devices	3.5. Exposure to nanomaterials from medical devices Page 20 line 15 -20 Although humans may be exposed to nanomaterials from medical devices it is also possible that devices may be designed and manufactured such that no nanomaterials are released. In this case only issues of local contact with tissues remain. It might be useful to mention this to encourage the development of stable devices and simplify the regulatory process in these cases. Section 5 "Summary" seems to consider this possibility stating Page 48 line 14-17 "If as a result of these studies, it is concluded that even under realistic worst-case use conditions particle release will be very low,	SCENIHR agrees with the comment. However, this aspect is clearly addressed in the Guidance on page 24 in Table 3 where possible exposures are indicated. This table also contains fixed nanomaterials in non-degradable medical devices. This is also addressed in section 5.

			no further consideration of the risk should be required. Further considerations are needed when a substantial release is noted".	
52	Dahms Janell, 3M/3M ESPE Dental Products Division, jkdahms@mmm.com, United States	3.5. Exposure to nanomaterials from medical devices	Lines 28-29 "The intended use of therapeutic devices, sensors/diagnostics for in vivo use, regenerative medicine, and implants. inherently implies high exposure potential for patients." While exposure to the device itself may be inherently high, it does not follow that potential exposure to a nanomaterial used in the device will be inherently high. The exposure potential for a nanomaterial that is present at a very low concentration in a device or which is strongly bound within the device would be inherently low.	SCENIHR agrees with the comment. However, this aspect is clearly addressed in the Guidance on page 24 in Table 3 where possible exposures are indicated. This table also contains fixed nanomaterials in non-degradable medical devices. This is also addressed in chapter 5.
53	Stock Gregor, FIDE - Federation of the European Dental Industry, g.stock@fide-online.org, Germany	3.5. Exposure to nanomaterials from medical devices	In line 18-19 wear processes are mentioned as source of nanoparticles. In some applications medical devices must be grinded or polished or shaped during application. This is another source of nanomaterial formation. This source being very important for some groups of medical devices (e.g. dental fillings) it is recommended to add it to the list. In line 13 – 20 there is a discussion on exposure to free nanomaterials from medical devices. Otherwise in the Introduction (page 10, line 39) dental filling materials are mentioned as example for such free nanomaterials. For dental filling materials it	Line 18-19. SCENIHR agrees with the comments. Text was added on page 20, line 16, indicating the grinding/polishing of dental materials as another source of the release of nanomaterials. "In addition, in some applications medical devices must be grinded, polished or shaped during application (e.g dental fillings), which may also be a source for the release of nanomaterials." Line 13 – 20. SCENIHR agrees with the comment. Text has been added to page 21 before line 18.

			should be considered that they fall in the category of free nanomaterial containing medical devices only in their paste form (as applied to patient). After a very short exposure time the dental filling materials are cured (e.g. by light) and become medical devices containing firmly bound nanomaterials. Similar situation is present in other medical devices too (e.g. bone cements, tissue glues …). For this reason we suggest to add before the sentence starting in line 18 a phrase mentioning this special but not rare case. Should be added in line 18: There are medical devices that can be regarded as containing free nanoparticles during a very short exposure time, the longest exposure time during their life cycle they are devices containing firmly bound nanomaterials (e.g. dental fillings or bone cements that are cured during application switching from a paste to s solid form). In line 21 – 27 a large number of nanomaterials are enumerated. Two important groups of nanomaterials that are used in many medical devices are missing: pigments (that, for obtaining a good shading of products, are mostly very small particles) and ordinary fillers (that due to the small amount of fine (nano)particles by weight can easily fall under the nanomaterial definition (particle distribution)).	"It should be noted that there are medical devices that can be regarded as containing free nanoparticles during a very short exposure time, the longest exposure time during their life cycle they are devices containing firmly bound nanomaterials (e.g. dental fillings or bone cements that are cured during application switching from a paste to a solid form)." Line 21 – 27 SCENIHR agrees with the comment. Text has been added to page 20 line 27. "Other groups of particles used in medical devices that may contain nanomaterials are pigments and fillers."

			It would be important to mention these types as well, being one of the major sources for nanomaterials according to the EU definition in many medical devices.	
54	FLAMENT Guillaume, Nanotechnology Industries Association (NIA), guillaume.flament@nanotechia.org, Belgium	3.5. Exposure to nanomaterials from medical devices	The complete absence of release is impossible to demonstrate scientifically. Also, the regulatory framework is, at the moment, unclear on the 'release' criteria: in the European Parliament's amended version, only devices in which nanomaterials are deliberately intended to be released are concerned by Class III classification [1]. [1] Amendment 304 European Parliament legislative resolution of 2 April 2014 on the proposal 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)0542 – C7-0318/2012 – 2012/0266(COD)) (Ordinary legislative procedure: first reading)	SCENIHR agrees with the comment. In this Guidance SCENIHR wants to indicate that in the risk assessment potential particle release should be considered and if possible determined. The chapter on exposure i.e. particle release does not indicate a risk classification.
55	king mel, mhra, , United Kingdom	3.5.1. Release of nanomaterials from medical devices	3.5.1. Release of nanomaterials from medical devices Page 21: On page 21 of the paper the authors list three possibilities where nanomaterials have the potential to be released. MHRA are of the Opinion that the second possibility is a subset of the third possibility. For example coatings such as	Chapter 3.5.1 indicates that for the exposure assessment the possibility of potential release of nanomaterials from a medical device should be considered. The outcome might be that there is no release due to, for example, strong bonding or integration in a material matrix. SCENIHR disagrees with the comment that the

			those found in hip implants are usually removed through wear following contact between the two artificial surfaces. Page 21 Line 14 to 16: The fourth possibility is that there is no or very low release of nanomaterials. If this can be demonstrated the regulatory process would be simplified. Perhaps this section should consider this possibility. This possibility is considered elsewhere in the Preliminary Opinion. Section 5 "Summary" seems to consider this possibility stating (Page 48 line 14-17) "If as a result of these studies, it is concluded that even under realistic worst-case use conditions particle release will be very low, no further consideration of the risk should be required. Further considerations are needed when a substantial release is noted".	second possibility is a subset of the third possibility. The second possibility addresses the situation in which the nanomaterials themselves are used as medical device (e.g. iron nanoparticles for heat therapy) and are injected as free nanoparticles. The third possibility addresses the issue of the use of free nanomaterials in or on a medical device. So, there is an essential difference in the potential for exposure. Text has been added to page 21 before line 18. "When there is a strong bonding on the medical device surface or the nanomaterials are firmly incorporated in the matrix of a (bio)material no or negligible release may occur."
56	Dahms Janell, 3M/3M ESPE Dental Products Division, jkdahms@mmm.com, United States	3.5.1. Release of nanomaterials from medical devices	Lines 26-29 "For materials that intentionally or unintentionally degrade upon tissue contact, particles will ultimately be formed as a result of mechanical collapse, which may cause nanoparticles to be generated from either the bulk material or nano-sized components." Since most materials used in medical devices eventually degrade to some extent on prolonged tissue contact, historical safety data for medical devices of this type would suggest that, with some exceptions, release of nanoparticles from medical devices does	This may indeed be so. However, SCENIHR cannot (and will not) publish such a statement without a proper scientifically sound reference to substantiate this statement.

			not pose a significant health risk for patients.	
57	Dahms Janell, 3M/3M ESPE Dental Products Division, jkdahms@mmm.com, United States	3.5.1. Release of nanomaterials from medical devices	Lines 37-38 "Because there are no occupational exposure limits for nanoparticles." NIOSH has established OELs for nanoscale titanium dioxide and carbon nanotubes and fibers. Some nanomaterial manufacturers have established occupational exposure guidelines for their products based upon toxicity test data. It is also worth noting that routine measures for infection control (e.g., use of gloves, masks, and eye protection) may limit exposure of dental professionals to nanomaterials produced by polishing and grinding.	Agreed. The text is adapted accordingly. Page 21, lines 37-38. "There are only a limited number of occupational exposure limits for nanoparticles (e.g. nanoscale TiO2 , carbon nanotubes and fibers, NIOSH 2011, 2013). So, it is not possible to speculate on relative health associated risks from nanoparticles released when grinding or polishing dental composites."
58	Dahms Janell, 3M/3M ESPE Dental Products Division, jkdahms@mmm.com, United States	3.5.1. Release of nanomaterials from medical devices	Lines 34-37 "Particles in the nano-size range have been detected in debris after grinding or polishing dental composites on a laboratory surface as well as in the aerosol after polishing of nano-composite restorations in the front teeth Van Landuyt et al., 36 2012, 2014; Kostoryz et al., 2007)." Add parenthesis preceding Van Landuyt. The work of Bogdan et al 2014 should be cited in this context. Also, the citation of Kostoryz 2007 refers to a presentation on cytotoxicity of nanomaterials presented at a conference/trade show and a detailed description of this work does not appear to be published in a peer-reviewed journal. The	SCENIHR agrees with the comment and the reference to Kostoryz et al 2007 is deleted. Bogdan et al., 2014 was added to the text and reference list.

			presentation abstract refers to “dental nanocomposite dust” but there is no indication of 1) the methods used to generate or characterize the dust or 2) the characteristics of the dust. We recommend that the reference to Kostoryz et al. 2007 be deleted.	
59	Stock Gregor, FIDE - Federation of the European Dental Industry, g.stock@fide-online.org, Germany	3.5.1. Release of nanomaterials from medical devices	Nanomaterials generated by wear do not necessarily contain those nanomaterials in their original form that have been put into the medical device during production. When they are released by wear they may be covered with material form the matrix (Bogdan et al., 2014). The biological reaction to these nanomaterials may be totally different to the original nanomaterials (Smulders et al., 2014) We would also like to point out that exposure to nanomaterials from grinding or polishing of dental medical devices lasts only a few minutes for each restoration. It is only a short term exposure. Below line 17: As mentioned in our comments to the exposure chapter (page 20, line 18-19) there is an additional process for nanomaterial release: the intra-operative grinding, polishing or shaping of medical devices that can lead to a release of nano-dust independent if the medical device contained or not nanoparticles. A corresponding phrase should be added Paragraph of lines 30 – 40 and 41	SCENIHR agrees with the comment. The text has been adapted. The released nanosized materials do not necessarily contain the original nanomaterials present in the medical device. They may be covered with material from the matrix (Bogdan et al., 2014). In addition, when incorporated in a matrix, nanomaterial toxicity may be different from the toxicity of the original pristine nanomaterial (Smulders et al., 2014). Below line 17. The issue of generation of nanosized dust/wear from medical devices not produced with nanomaterials has already been addressed several times in the Opinion. Paragraph of lines 30 – 40 and 41 – 51. The text was kept as it is. Grinding can be considered as belonging to the use of the medical device, so a characteristic of its use. Wear comes after the placing of a medical device. So, the order is first degradation,then wear due to placing (i.e

			– 51: If the grinding, polishing, shaping processes are added as an own source of nanomaterial release (as proposed above) the two paragraphs should be interchanged to have the same order as above (first wear, than grinding, shaping).	grinding/polishing), and lastly. wear due to the passing of time. Also text added on release of nanomaterials from composites. Based on comment no.92. “Nanoparticles may be generated through abrasive wear or grinding of a material (Frogget et al., 2014). Several scenarios could be identified for nanoparticle release including machining, weathering, washing, contact and incineration (Frogget et al., 2014). Identified debris were particles from matrix alone, matrix particles with the nanomaterial embedded, the nanomaterials themselves or dissolved ionic forms of the added nanomaterial.”
60	Sanak Aleksandra, Council of European Dentists (CED), ced@eudental.eu, Belgium	3.5.1. Release of nanomaterials from medical devices	Lines 20 - 40: The CED shares SCENIHR's Opinion that medical devices not containing nanomaterials can generate nanoparticles as a result of wear-and-tear. The approaches indicated in the preliminary Opinion may also be applicable for such wear-and-tear generated nanoparticles.	SCENIHR agrees with the comment and thanks the CED.
61	Dahms Janell, 3M/3M ESPE Dental Products Division, jkdahms@mmm.com, United States	3.5.2. Exposure of patients to nanomaterials released from medical devices	Lines 28-29 “Products consisting of free nanomaterials always lead to high potential for systemic exposure…". We suggest removing the words “high” and “always” from this sentence. As mentioned in the next sentence in the SCENIHR document, whether or not a high systemic exposure occurs depends on various factors including	SCENIHR partly agrees with the comment. The text is meant as a kind of introduction raising the awareness when free nanomaterials are use or present. And indeed whether a release occurs is dependent on the use of the medical device. The word “always” is deleted.

			the actual use of the medical device and the route of exposure. The quantity of free nanomaterials in the device and the physicochemical properties of the nanomaterial will also influence the potential for systemic exposure.	
62	Dahms Janell, 3M/3M ESPE Dental Products Division, jkdahms@mmm.com, United States	3.5.2. Exposure of patients to nanomaterials released from medical devices	Lines 43-44 In particular for dental fillings, exposure may also occur during polishing. (Van Landuyt et al., 2014). Text should be revised to include reference to the work of Bogdan et al. 2014.	SCENIHR agrees with the comment. Text dealing with this subject has been inserted in section 3.5.1 on page 21. On page 22 reference of Bogdan et al., 2014 was added after Van Landuyt et al., 2014).
63	Stock Gregor, FIDE - Federation of the European Dental Industry, g.stock@fide-online.org, Germany	3.5.2. Exposure of patients to nanomaterials released from medical devices	Line 5 indicates dental procedures as one major route of inhalative exposure. Due to the use of water spray during such procedures an inhalative exposure is of much lower probability as a mucosal or oral exposure. For this reason the example seems to be inappropriate. Dental procedures should be removed being not a typical example.	SCENIHR agrees with the comment. However, there is a possibility for inhalation exposure depending on the actual situation and dental procedures used. This is a Guidance document intending to raise awareness of the various situations in which exposure may occur. The text was not changed.
64	Sanak Aleksandra, Council of European Dentists (CED), ced@eudental.eu, Belgium	3.5.2. Exposure of patients to nanomaterials released from medical devices	Line 5: Regarding the uptake via inhalation from dental products, it should be asked if there have been any studies performed simulating dental procedures; like grinding and polishing ? If not this should be mentioned in the Opinion.	SCENIHR agrees with the comment. Text regarding studies on grinding and polishing are added on page 21, section 3.5.1. These studies demonstrate the release of nanosized material from grinding. So, there is a possibility for inhalation exposure depending on the actual situation and dental procedures used.

65	Dahms Janell, 3M/3M ESPE Dental Products Division, jkdahms@mmm.com, United States	3.5.3. Exposure of professional users to nanomaterials released from medical devices	Lines 6-7 “Exposure may occur especially during polishing of dental fillings (Van Landuyt et al., 2014).” Text should be revised to include reference to the work of Bogdan et al. 2014.	SCENIHR agrees with the comment. Text dealing with this subject has been inserted in section 3.5.1 on page 21. On page 23 section 3.5.3 reference of Bogdan et al., 2014 was added after Van Landuyt et al., 2014).
66	Stock Gregor, FIDE - Federation of the European Dental Industry, g.stock@fide-online.org, Germany	3.5.3. Exposure of professional users to nanomaterials released from medical devices	Line 9 indicates dental procedures as one major route of inhalative exposure. Due to the use of water spray during such procedures an inhalative exposure is of much lower probability as a mucosal or oral exposure. For this reason the example seems to be inappropriate. Dental procedures should be removed being not a typical example. Line 14 -16 mentions nanomaterials produced by wear or other degradation processes. It must be considered that the nanoparticles released by such processes are not necessarily identical to the nanomaterials used in manufacturing of the devices. Sampling and characterization of such newly formed nanoparticles is extremely difficult because there are no good and reliable in vitro techniques available yet for simulating the wear or degradation process in vivo.	Line 9 SCENIHR agrees with the comment. However, there is a possibility for inhalation exposure depending on the actual situation and dental procedures used. This is a Guidance document intending to raise awareness of the various situations in which exposure may occur. The text was not changed. Line 14 -16 Text dealing with this subject has been inserted in section 3.5.1 on page 21.
67	Sanak Aleksandra, Council of European Dentists (CED),	3.5.3. Exposure of professional users to nanomaterials	Lines 4 - 9: Regarding the uptake via inhalation from dental products, it should be asked if there have been any studies performed simulating dental procedures, like	SCENIHR agrees with the comment. Text regarding studies on grinding and polishing are added on page 21, section 3.5.1. These studies demonstrate the release of nanosized material from grinding. So,

	ced@eudental.eu, Belgium	released from medical devices	grinding and polishing ? If not, this should be mentioned in the Opinion.	there is a possibility for inhalation exposure depending on the actual situation and dental procedures used.
68	king mel, mhra, United Kingdom	3.5.4. Estimation of exposure for risk assessment	3.5.4. Estimation of exposure for risk assessment Page 24 Lines 1 -3 The first sentence of page 24 it would be important to qualify what the authors mean by "quality". It is not obvious what parameters they refer to which would designate a material as good or bad quality. Page 24 table 3 MHRA are not really sure what the benefit of having Table 3 on page 24 is or how the authors came to propose these exposure estimates. Neither is there an explanation of all terms for example what is meant by M/M or N/N or what the authors mean by high, medium or low exposure.	Page 24 Lines 1 -3 What is meant is the resistance against wear and tear. This has been added to the text for clarification. "In addition to the potential (bio)degradable property of a material , the "quality" of the material used to manufacture a medical device should be considered in terms of possible resistance against wear and tear." Page 24, table 3. Table 3 is included to help risk assessors in the estimation of exposure scenarios for medical devices. As medical devices comprise a very broad range of products, this table helps to categorise exposures depending on the type, use and application time of medical devices. M/M and N/N are explained by the example H/L.
69	king mel, mhra, United Kingdom	3.6. Toxicokinetics	3.6. Toxicokinetics Page 25 line 5 (general comment) Toxicokinetics of nanomaterials and their metabolic fate is discussed at length, but it is important to note that the results obtained maybe irrelevant to ultimate product performance depending on the final composition of a Medical Device/Medicinal Product, proposed use-clinical setting, patient population, route and frequency of	SCENIHR agrees with the comment. The evaluation of toxicokinetic profile of nanomaterials is discussed in general. Indeed there may be clinical situations in which medical devices/medicinal products are used for which toxicokinetics and/or toxicity is less relevant. This is true for any step of the risk assessment process: it is always possible to ask for derogation in presenting data or studies, but a scientifically

			administration and in certain cases the external trigging device used to activate. Example: A product intended for use in patients with poor prognosis might require less investigation than one intended for long-term management of a chronic condition. It is understood that Magforce's NanoTherm has been used in the treatment of glioblastoma: a condition with an average life expectancy of under 1 year*. The clinical setting and patient population may have been taken into account in the risk assessment. *"NanoTherm's CE mark in 2010 was for treatment of brain cancers, including glioblastoma, and the clinical evidence from a Phase II, 59-patient study of the therapy was strong, believes Dr Lipps. "There were patients with recurring glioblastoma who essentially had around 13 additional months of life [after being treated with NanoTherm] versus historic controls, which had around six additional months – the company really had a very good product." (http://www.clinica.co.uk/marketsector/other/INTERVIEW-MagForce-turns-the-heat-up-on-NanoTherm-cancer-therapy-push-353329) Page 25 line 34 The statement "rapid clearance of the nanoparticles from the blood is mainly into the liver and spleen" should be qualified as this is not always the case. The	based justification should be provided. For the treatment of tumours, kinetics are important in order to evaluate whether the product reaches the tumour. As this is a general Guidance such specific situations (e.g treatment of terminal patients) are not considered. Page 25 line 34. SCENIHR agrees with the comment. The text has been adapted to emphasize that this is a general statement. As medical devices should be evaluated on a case-by-case basis, this exception has not been added. Text has been changed: "In general, the clearance of the nanoparticles from the blood is mainly via the liver and spleen (…)".

			route of elimination must be defined on a case-by-case basis.	
70	Dahms Janell, 3M/3M ESPE Dental Products Division, jkdahms@mmm.com, United States	3.6.1. Introduction	Lines 14-15“ For subgroups of certain solid nanomaterials, it is doubtful whether metabolism (M) really occurs.” Several studies have reported metabolism of nanomaterials including magnetite dextran, surface-treated metals, and surface-modified single-walled carbon nanotubes (reviewed in Landseidel et al. 2012). Due to copyright restrictions, the followingis provided in lieu of upload of paper: Landsiedel R, et al. (2012). Toxico-/biokinetics of nanomaterials. Arch. Toxicol. 86, 1021-1060.	SCENIHR agrees with the comment. Also Landsiedel et al, 2012 indicate that metabolism seldom occurs. Text has been added with the reference of Landsiedel et al., 2012.
71	Berzanskis Laurel, Health Care Without Harm Europe, laurel.berzanskis@hcwh.org, Belgium	3.6.2. Methods to evaluate toxicokinetics of nanomaterials	Page 26, line 10-11 - Add in the paper that the development of nanospecific methodologies should be mandated.	SCENIHR is an advisory committee regarding risk assessment and safety of various subjects. The Guidance discusses potential pitfalls when testing nanomaterials. It also indicated where possible adaptations of the used assays may be needed (e.g. prolonged studies for toxicokinetics/clearance). Whether adaptations specific techniques should be mandated and by whom is not within the scope of this Opinion. Some text has been added in the Abstract and section 5 Summary and Conclusions. “For some assays evaluating potential hazards of nanomaterials adaptation of existing assays may be necessary.”

72	king mel, mhra, , United Kingdom	3.6.2. Methods to evaluate toxicokinetics of nanomaterials	3.6.2. Methods to evaluate toxicokinetics of nanomaterials Page 26 line 26- 27 An example of “a single and repeated kinetic” study to assess distribution and persistence of iron nanoparticle may be found in the following reference: Elford, P., et al., Biodistribution and predictive hepatic gene expression of intravenous iron sucrose, Journal of Pharmacological and Toxicological Methods (2013), http://dx.doi.org/10.1016/j.vascn.2013.04.005 Guidance on conduct of distribution studies is provided in Section 2.2.2 “Bio-distribution studies” in Reflection paper on the data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product (.EMA/CHMP/SWP/620008/2012) http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500149496&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc) See also section 3.2.3 non-clinical studies in Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product, EMA/CHMP/806058/2009/Rev. 02,	Page 26 line 26- 27 Examples are already included. The reference of Elford et al., 2013 is not added because only a single IV administration was used in this paper. Page 26 Line 36 -37. SCENIHR agrees with the comment. The development of single particle ICP-MS now opens the possibility of detecting particles in complex matrices including tissues. Although not much information is available at the moment, a reference to sp ICP-MS is included (Van De Zande et al., 2012).

			http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/03/WC500140351.pdf) Page 26 Line 36 -37 It is agreed that "the detection of nanoparticles in tissues/organs is complex". There appears a widening gap between nanomaterial applications/products and techniques to detect and quantitate, them especially in-vivo. Elsewhere in the document " "particle persistence" is mentioned (see Chapter 4 Risk Evaluation page 44). If it can be demonstrated that the particle is not persistent perhaps the difficulties in detecting an intact nanoparticle in-vivo might be avoided.	
73	Dahms Janell, 3M/3M ESPE Dental Products Division, jkdahms@mmm.com, United States	3.6.2. Methods to evaluate toxicokinetics of nanomaterials	Lines 12-18 "For a dissolved chemical, the tissue uptake and release is generally dependent on the blood concentration (when excluding specific active transport, the first-pass effect in the liver and highly bioaccumulating chemicals in the adipose tissue) and an equilibrium between blood and organ concentration is generally obtained. This is because nanoparticle uptake in organs occurs rapidly and a repeated administration results in an increase of nanomaterials, predominantly in the liver and spleen after intravenous administration (Lankveld et al., 2010)." There is something missing between these two sentences – the second does not follow	Lines 12-18 SCENIHR agrees with the comment. A word was changed in the final editing. The original text was: "For nanoparticles uptake in organs occurs rapidly and a repeated administration results in an increase of nanomaterials, predominantly in the liver and spleen after intravenous administration (Lankveld et al., 2010)." Text has been changed accordingly. "Nanoparticle uptake in organs occurs rapidly and a repeated administration results in an increase of nanomaterials, predominantly in the liver and spleen after intravenous administration (Lankveld et

			from the first. Also, the second sentence is an overly broad generalization. The biokinetics of particular nanomaterials are strongly influenced by a number of factors including size, surface charge, protein binding, and solubility (reviewed in Landsiedel et al. 2012). Due to copyright restrictions, the following is provided in lieu of upload of paper: Landsiedel R, et al. (2012). Toxico-/biokinetics of nanomaterials. Arch. Toxicol. 86, 1021-1060.	al., 2010)." The following text has been added to reflect the influences on biodistribution. "The biodistribution of nanoparticles is influenced by a number of factors, including for example size, surface charge, and surface composition like protein binding and coating (De Jong et al., 2008, Lankveld et al., 2011, Landsiedel et al., 2012)."
74	Dahms Janell, 3M/3M ESPE Dental Products Division, jkdahms@mmm.com, United States	3.6.2. Methods to evaluate toxicokinetics of nanomaterials	Lines 31-32 "Release/elimination from an organ seems to be associated with a possible dissolution or degradation of the nanomaterials." Clearance can also occur as a result of uptake by resident macrophages and transport to the lymphatic system. (reviewed in Landsiedel et al. 2012). Due to copyright restrictions, the following is provided in lieu of upload of paper: Landsiedel R, et al. (2012). Toxico-/biokinetics of nanomaterials. Arch. Toxicol. 86, 1021-1060	SCENIHR agrees with the comment. Text has been added to reflect possible excretion. Lines 31-32 "For some nanomaterials (quantum dots. Polystyrene nanoparticles, MWCNT) excretion was demonstrated by the kidney and or liver (Landsiedel et al., 2012)."
75	FLAMENT Guillaume, Nanotechnology Industries Association (NIA), guillaume.flament@nanotechia.org,	3.6.2. Methods to evaluate toxicokinetics of nanomaterials	Nanosilver particles are not intended to be released into the body but they are embedded inside the material. Similarly to microsilver, silver salts or silver electrodes, nanosilver releases silver ions; the anti-microbial effect of nanosilver is ion-related	SCENIHR agrees with the comment. However, even when there is no intention for the release of nanosilver, toxicokinetic studies should be considered.

	Belgium		and not nano specific.	
76	Dahms Janell, 3M/3M ESPE Dental Products Division, jkdahms@mmm.com, United States	3.6.4. Invasive medical devices	Lines 12-26 "Uptake after inhalation exposure (e.g. related to dental procedures)" The studies referenced in this paragraph examined the behavior of aluminum oxyhydrides, pigment grade iron oxide, lanthanum-labeled metal oxides, gold nanoparticles, and gold nano-agglomerates. Although the paragraph heading has specifically referenced dental procedures, it appears that few of the materials studied are directly relevant to exposure via the dental composites repeatedly referenced elsewhere in the draft Opinion. Current understanding indicates that behavior of nanoscale materials in biological systems is highly dependent on the specific physicochemical characteristics of the nanomaterial, and that any extrapolation to other materials must be done with care. For example, this Opinion states on Page 11, Lines 23-24 that extrapolation from one nanomaterial to another is not possible. As such, the generalizations in this paragraph should be clarified in regard to exposure via dental procedures.	SCENIHR agrees with the comment. The examples mentioned are specific with regard to the possible toxic effects of nanomaterials on the lung. Indeed the materials mentioned are not commonly used in dental materials. These phenomena might also occur after inhalation of fractions of dental materials. Text has been added to reflect that the information provided is for inhalation toxicity of nanomaterials in general. "The effect of particles on the lung is quite well known and many inhalation studies have been performed with nanomaterials."
77	Dahms Janell, 3M/3M ESPE Dental Products Division,	3.6.4. Invasive medical devices	Lines 20-22 "In addition, inhaled nanomaterials may migrate into the brain via the olfactory nerve (Oberdörster et al., 2004, Balasubramanian et al., 2013)." This was	SCENIHR agrees with the comment. The word "certain" has been added.

	jkdahms@mmm.com, United States		shown to occur only for certain types and sizes of nanomaterials. The word “certain” should be added before “inhaled nanomaterials.”	
78	Schmidt Cathrine, Bayer HealthCare, cathrine.schmidt@bayer.com, Germany	3.6.4. Invasive medical devices	Comment on the definition of nanomaterials and application to non biopersistent nanosomes / nanoemulsion: It is of our Opinion that nanosomes or nanoemulsion for topical application and not biopersistent should not be considered as nanomaterials as defined in the proposed regulation and the proposed Opinion. In 3.6.4 Invasive medical devices, it is stated “ nanoparticles such as liposomes, micro/nanospheres, microemulsions, and dendrimers (Honda et al., 2013)”. However, substances that are present in form of nanoemulsions and nanosomes in Finished Products for Topical use which are soluble when applied on the skin, are losing the nanoform as soon as applied on the skin. Indeed the droplets or capsules formed by the nanosomes break directly at the application to the skin. The nanoproperties are therefore disappearing directly at the application of the product. There is no dermal penetration of nanoparticles and no possible uptake. Later in paragraph 3.7.3.1, it is stated “unlike solubilised chemicals, nanomaterials generally exist as a suspension/dispersion of	SCENIHR partly agrees with the comment. 3.6.4 page 28. In the preparations the products do have a nanoformulation. Also EMA uses a much broader size range specifically to include the liposomal preparations of which the size is often in the 200-300 nm range. Indeed these preparations need to be solubilised as they are used for drug delivery on the eye. Text has been added for clarification. “The nano-aspect of these products may disappear after application.” Whether some terminology like “insoluble or biopersistant” should be included in the new medical device regulation is not an issue for SCENIHR.

			insoluble or partially-soluble nanoparticles and/or larger agglomerates and aggregate". According to this statement, nanosomes and nanoemulsion which are totally soluble in the skin are not considered as nanomaterials.This should be taken into account. Furthermore it is to be noted that the nanomaterial definition in the the EU cosmetic products regulation does exclude nanosomes and nanoemulsions, where it states that a nanomaterial is an "insoluble or biopersistant" material. This should be implemented in the medical devices regulation as well.	
79	Sharma Monita, PETA International Science Consortium, Ltd., , monitas@piscltd.org.uk, United Kingdom	3.7.1. Introduction	PAGE#29 Line# 40-44. "There are ongoing developments in in vitro methods, but currently there are no validated in vitro methods for hazard assessment of nanomaterials (Park et al., 2009, Cockburn et al., 2012, Doak et al., 2012, Nel et al., 2013a). However, in vitro tests may be useful for screening purposes, and to elucidate possible mode of action (Basketter et al., 2013, Nel et al., 2013b), but their use should be evaluated on a case-by-case basis." In addition to their use as screening purposes, in vitro tests can be used to study more complex physiological endpoints such as inflammation, fibrosis, and formation of epithelioid granulomas to assess inhalation exposure to nanomaterials (Sanchez, Weston	SCENIHR agrees with the comment. Text has been added. "Also for the induction of fibrosis and epitheloid cells by high aspect ratio HAR nanomaterials (e.g. some CNTs) models have been developed to study the mechanisms of nanomaterial cell interaction (Sanchez et al., 2011,Vietti et al., 2013)." PAGE#30 Line# 2 Text has been added and modified according to the comment. "In a recent review some obstructions were identified for the use of QSAR techniques in nanotoxicology (Winkler et al., 2013). They stated the following on the use of in silico techniques.

			et al. 2011; Vietti, Ibouraadaten et al. 2013). A tier based strategy can be devised for hazard assessment of nanomaterials using in vitro methods where simpler tests (such as acellular and single cell cultures) can provide a good indication of potential overt toxicity of nanomaterials and can be used as a first tier for prioritizing the need for further testing at higher tier levels using more complex in vitro systems. Such a decision-based tiered approach could be combined with the available information to assess the effects of nanomaterials. One example of such an approach is described in the OECD's 'New Guidance document on an integrated approach on testing and assessment (IATA) for skin corrosion and irritation (Online at: http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2014)19&doclanguage=en). PAGE#30 Line# 2. "However, they are unlikely to be useful in the foreseeable future for the assessment of relevant toxicological endpoints that are needed for risk assessment." In silico approaches are still being developed but with the increased understanding of the bioeffects of nanomaterials, development of alternative testing strategies and focused efforts towards data storage and sharing it is possible to implement predictive modeling to	"Three of the major roadblocks to applying QSAR methods to modelling biological properties of nanoparticles are insufficient experimental data on the composition of the bio-corona on nanoparticle surfaces, the lack of in vitro data predictive of in vivo effects of nanomaterials, and the paucity of 'nanoparticle-specific' descriptors."(Winkler et al., 2013). So, there is indeed some progress in the development of in silico models however, . . . ".

			assess toxicological effects of nanomaterials that are relevant for risk assessment (Winkler, Mombelli et al. 2013). We recommend adding Winkler, et al., to the references to provide the state-of-the-science for in silico approaches and a proposed timeline and requirements for their implementation for the assessment of relevant toxicological endpoints that are needed for risk assessment. Sanchez, V. C., P. Weston, et al. (2011). "A 3-dimensional in vitro model of epithelioid granulomas induced by high aspect ratio nanomaterials." Part Fibre Toxicol 8: 17. Vietti, G., S. Ibouraadaten, et al. (2013). "Towards predicting the lung fibrogenic activity of nanomaterials: experimental validation of an in vitro fibroblast proliferation assay." Part Fibre Toxicol 10: 52. Winkler, D. A., E. Mombelli, et al. (2012). "Applying quantitative structure-activity relationship approaches to nanotoxicology: Current status and future potential." Toxicology 313(1): 15-23.	
80	Dahms Janell, 3M/3M ESPE Dental Products Division, jkdahms@mmm.com, United States	3.7.2. Potential pitfalls in toxicity testing of nanomaterials	Lines 27-30 “It is important to consider if vehicle and/or the test or cell culture medium does not modify the physicochemical properties (including adsorption of biomolecules on the surface) of the nanomaterial tested because it may influence general toxicity.” It is hard to	SCENIHR agrees with the comment. Some explanatory text has been added. Lines 27-30. “Therefore a proper characterisation under dosing/test conditions is needed. In addition, it

			imagine a case in which the surface properties of a nanomaterial would not be altered by placing it in a dose vehicle or cell culture medium. Therefore, it is important to characterize the properties of the nanomaterial in the vehicle or medium used and to consider how these properties might influence the study results and how they compare to the properties of the nanomaterial in exposed patients.	is……"
81	Monita Sharma, PETA International Science Consortium, Ltd., , monitas@piscltd.org.uk, United Kingdom	3.7.2. Potential pitfalls in toxicity testing of nanomaterials	PAGE#30 Line# 13-20. "Testing of insoluble or partially-soluble nanoparticles using in vivo or in vitro methods must also take into account that they will be present in a dosing or test medium as a nano-dispersion rather than in solution. Therefore, any toxicity testing using in vivo and in vitro methods should pay special attention to the agglomeration/aggregation behaviour, and the insoluble/ partially-soluble nature of nanomaterials (SCENIHR, 2009;Kreyling et al., 2010, EFSA 2011, SCCS 2012). Possibilities for disagglomeration of nanomaterial should also be considered. During toxicological evaluations, some properties of nanomaterials may change due to interaction with the surrounding media." Dissolution of nanomaterials is a complex phenomenon. In addition to the ionic fraction of nanomaterials, there is a possibility of	SCENIHR agrees partly with the comment. Maurer et al., indeed demonstrate the formation of new small silver nanoparticles/shapes. However, it is not clear from the paper, and indeed also not mentioned by the authors, whether these are the result of reformation of the nanoparticles from the dissolved silver ions. The text has been slightly modified to draw the attention to the possibility for re-aggregation of nanoparticles. "Possibilities for disagglomeration and re-aggregation of nanomaterials should also be considered." Line# 27-32. The OECD Guidance on sample preparation is cited below Table 1. Also text has been added on page 31 at the end of the section. "For the sample preparation and dosing of

			reformation of nanomaterials from the ions (Pal, Sau et al. 1997; Maurer, Sharma et al. 2014). Therefore, in addition to considering the possibility of disagglomeration of nanomaterial the possibility of reformation of nanomaterials should also be considered. These life cycle changes of nanomaterials (agglomeration/aggregation, disagglomeration and dissolution) can be assessed using in vitro methods such as incubation in physiologically relevant simulant fluids (Pal, Sau et al. 1997; Maurer, Sharma et al. 2014). PAGE#30 Line# 27-32. "It is important to consider if vehicle and/or the test or cell culture medium does not modify the physicochemical properties (including adsorption of biomolecules on the surface) of the nanomaterial tested because it may influence general toxicity. It is therefore important to ascertain the stability and uniformity of the nanomaterial in a test medium to ensure that the applied concentration/dose of nanomaterial is as assumed (Allouni et al., 2009)." The OECD Guidance on sample preparation and dosimetry (ENV/JM/MONO [2012] 40) should be referenced as an important resource (Online at:	nanomaterials the OECD has prepared a Guidance document (OECD 2012). Line# 37-44. Text modified according to comment. "Some of these problems might be overcome by either adding appropriate controls or modifying existing protocols. For instance, nanomaterials have been shown to interfere with the optical density readings for tetrazolium-based assays such as MTS and MTT; however, removal of nanomaterials via centrifugation before reading the assay can reduce the variations in data generated for the same nanomaterials (Xia et al., 2013, Ong et al.,14).

			http://search.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono(2012)40&doclanguage=en). PAGE#30 Line# 37-44. “Importantly, there may be an interaction between test reagents and the nanomaterials especially in colorimetric assays (such as sulforhodamine B dye, or MTT used in the viability assays). Moreover, some nanomaterials may themselves disperse/ absorb light and therefore, interfere with the measurements in colorimetric assays. These aspects need to be considered when using colorimetric methods. Produced proteins/biological mediators (e.g. cytokines) may also bind/adsorb on nanomaterial surfaces and may lead to low responses or even false negative results.” Potential nanomaterial interference can be overcome by either adding appropriate controls or modifying existing protocols. For instance, nanomaterials have been shown to interfere with the optical density readings for tetrazolium-based assays such as MTS and MTT; however, removal of nanomaterials via centrifugation before reading the assay reduced the variations in data generated for the same nanomaterials (Xia, Hamilton et al. 2013; Ong, Maccormack et al. 2014).	

82	king mel, mhra, , United Kingdom	3.7.3 Toxicity testing methods	3.7.3 Toxicity testing methods P33 and f Demonstrates the ways assessments can be done and a very thorough overview. To me, much can only be learned through clinical experience and meticulous reporting, I realise this may go beyond the brief for this paper. Will UDI cover nanotech at least when incorporated in devices? Gives potential for link to CPRD. Page 33 line 29 general comment The chapter on "Delayed-type hypersensitivity" appears to consider topical or dermal hypersensitivity reactions only. As this Preliminary Opinion provides Guidance on systemic exposure it might be expected that systemic hypersensitivity would be considered. This can be a most serious risk to public health so it is perhaps surprising that it is not addressed. There have been fatal hypersensitivity reactions associated with iron-nanocolloids. These have largely been attributed to the choice of carbohydrate polymer complexing agents used. On the 7th August 2014 new advice was issued for Rienso (ferumoxytol) to mitigate the risk of serious hypersensitivity reactions in the wake of post marketing data (see Dear Healthcare Professional letter: http://www.mhra.gov.uk/home/groups/comms-	SCENIHR agrees partly with the comment. Page 33 line 29 general comment. Indeed the sensitization assays are currently only focused on delayed type hypersensitivity. SCENIHR agrees that systemic hypersensitivity due to IgE can have more serious effects for example including anaphylactic shock. However, there are no toxicological tests available for evaluation of systemic immediate type hypersensitivity as it can be induced for example by protein antigens. Text has been added: "For certain iron nanoformulations after intravenous administration systemic allergic responses were observed as reported in an assessment report by EMA (EMA 2013). "

			ic/documents/drugsafetymessage/con454358.pdf). The EMA 's Committee for Medicinal Products for Human Use (CHMP) also published an Article 31 review (EMEA/H/A-31/1322) on the safety of intravenous iron products with regard to hypersensitivity reactions particularly in respect to pregnancy. All such products are iron oxide or oxyhydroxide nanoparticles with polymeric carbohydrate complexing agents (e.g. Iron Dextran). The Guidance document could perhaps draw attention to this work performed by the EMA with regard to the safety of these products and the need to considered hypersensitivity reactions if systemic exposure occurs. (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Intravenous_iron-containing_medicinal_products/human_referral_000343.jsp&mid=WC0b01ac05805c516f)	
83	Monita Sharma, PETA International Science Consortium, Ltd, monitas@piscltd.org.uk, United Kingdom	3.7.3 Toxicity testing methods	PAGE#36 Repeated-dose toxicity The European research initiative SEURAT (Safety Evaluation Ultimately Replacing Animal Testing) suggested in its annual report titled 'Towards the replacement of in vivo repeated dose systemic toxicity testing" that in vitro models, such as primary human hepatocytes and human iPSC-derived cardiomyocytes, can predict dose- and effect-additivity of a	SCENIHR agrees partly with the comment. Page 36. However, dose and effect additivity is not the subject of the section. In addition, the SEURAT initiative annual report gives results of research projects, which may be indicative, but they are far to be accepted at regulatory level. Page 37 line 20-25. SCENIHR is aware of the possibilities to evaluate the

			chemical given several concentrations and time-points are tested (Klein, Serchi et al. 2013). Page# 37 Repeated-dose toxicity Line # 20-25. “In any of the oral administrations mentioned above, one has to consider that the passage through the acid environment of the stomach and mixing with the chyme in the gut may affect the nanomaterial. Consideration of the potential for time dependent dissolution/ degradation is essential, as is the consideration of physico-chemical nanomaterial modifications such as agglomeration and surface modifications by proteins and biomolecules.” Physiological conditions of the gastrointestinal tract (e.g., pH) and their effect on physico-chemical properties of nanomaterials (e.g., agglomeration and dissolution) should be considered to assess nanomaterial impact after ingestion. However, these parameters can be assessed using acellular in vitro digestion assays using simulated gastric fluids (Wang, Nagesha et al. 2008; Wiecinski, Metz et al. 2009; Rogers, Bradham et al. 2012; Mwilu, El Badawy et al. 2013). In addition to exposing nanomaterials to simulated gastric fluids separately, there are systems that simulate sections of the gastrointestinal system, from the mouth to intestine, to allow sequential exposure of test	fate of nanoparticles in simulated gastric fluids and GI-tract models. Text is added to indicate the possibility for in vitro evaluation of nanoparticle changes due to GI-tract fluids. “The fate of nanoparticles in the gastro-intestinal tract can be investigated in in vitro models using simulated fluids or more complex systems (Minekus et al., 1999, Oomen et al., 2004) and has also been applied to nanoparticles (Rogers et al., 2012, Peters et al., 2012, Mwilu et al., 2013). Regarding the application of cell-based 3-D models the information is yet limited. So far they are mainly used for hazard identification (e.g the 3-D skin model for skin irritation).

			materials to different compartments (Minekus, Smeets-Peeters et al. 1999; Blanquet, Zeijdner et al. 2004). These systems can be useful in studying how nanomaterials are affected by different conditions that change substantially from one compartment to another. Additionally, human cell-based three dimensional tissue models are commercially available (such as MatTek's EpiIntestinal) which may also be applicable to nanomaterials. Furthermore, complex in vitro model systems such as the one developed under the InLiveTox project funded by the European Commission through the 7th Framework Programme, can be used to assess the systemic availability of nanomaterials after ingestion (Online at : http://www.inlivetox.eu/fileadmin/user/pdf/InLiveTox-Final_publishable_report.pdf). Minekus, M., M. Smeets-Peeters, et al. (1999). "A computer-controlled system to simulate conditions of the large intestine with peristaltic mixing, water absorption and absorption of fermentation products." Applied Microbiology and Biotechnology 53(1): 108-114. Mwilu, S. K., A. M. El Badawy, et al. (2013). "Changes in silver nanoparticles exposed to human synthetic stomach fluid: Effects of particle size and surface chemistry." Science of The Total Environment 447(0): 90-98. Rogers, K. R., K. Bradham, et al. (2012). "Alterations in	

			physical state of silver nanoparticles exposed to synthetic human stomach fluid." Science of The Total Environment 420(0): 334-339. Wang, L., D. K. Nagesha, et al. (2008). "Toxicity of CdSe Nanoparticles in Caco-2 Cell Cultures." J Nanobiotechnology 6: 11. Wiecinski, P. N., K. M. Metz, et al. (2009). "Gastrointestinal biodurability of engineered nanoparticles: Development of an in vitro assay." Nanotoxicology 3(3): 202-214. Please check the references	
84	king mel, mhra, , United Kingdom	3.8. Evaluation of nanomaterials used in medical devices	3.8. Evaluation of nanomaterials used in medical devices Page 40 Table 4 MHRA would be very cautious in proposing a specific framework for testing as that proposed in Table 4 on page 40. MHRA would not want this to be used as a checklist and in doing so discourage the manufacturer from carrying out a full risk assessments before embarking on testing. It is the manufacturer's responsibility to satisfy themselves that their device does not cause unnecessary toxicological risk to patients. In vivo testing should be a last resort after all other avenues have been explored which should include an assessment of available information from for example similar devices already on the market. This table appears to be suggesting for example invasive devices intended to be used for long term duration	SCENIHR agrees with the comment. It is also clearly stated that ISO 10993-1: 2009 applies. This standard is commonly used for the biological evaluation of medical devices, and indeed has a stepwise approach (starting with a literature search for already available information) while avoiding animal testing. The assays should be considered and are not intended as a checklist. Text added: "The schedule presented in Table 4 should not be considered as a checklist of assays to be performed but is intended as a Guidance to which assays have to be considered (in line with ISO 10993-1:2009) for the biological evaluation of a medical device containing nanomaterials. As for any step of the risk assessment process, it is always possible to ask for derogation in presenting toxicity studies, providing

			require a full battery of in vivo testing using countless animals without taking a weight of evidence approach and assessing the need for testing those applicable toxicological endpoints that have not been met by already available data. This approach is in keeping with the spirit of the 3R's for animal testing.	a scientifically based and sound justification is submitted".
85	Schmidt Cathrine, Bayer HealthCare, cathrine.schmidt@bayer.com, Germany	3.8.1. Non-invasive surface contacting medical devices	Comment on the definition of invasive versus non-invasive medical device: There is an inconsistent definition of non-invasive versus invasive medical device within the document and between the document and the MEDDEV guideline 2.4/1 Rev.9 on medical device classification. According to SCENHIR Opinion: Non-invasive medical devices, e.g. devices coming into contact with the intact skin, which is not breached and not compromised. Invasive devices (surgical or not), e.g.: - wound care materials, - implantable medical devices, - dental and bone fillings and cements, - injectable nanomaterials. However, in paragraph 3.6.3. "Toxicokinetics of nanomaterials present in non-invasive medical devices", example is given of a wound dressing device which is applied on a compromised skin although it is a non-invasive application. In paragraph, 3.8.1. Non-invasive surface contacting medical devices, it is stated that this category applies to devices that contact intact skin and breached or compromised surface.	SCENIHR disagrees with the comment. Wound dressing is both in 3.6.3 and in 3.8.1 indicated as a non-invasive medical device and can be used as such on breached skin. So, in the document it is consistent. In 3.8.2 it is indicated that when there is a possibility for systemic exposure (as it is in breached skin) additional testing for systemic toxicity may be considered. Even when a wound dressing by itself is a non-invasive medical device when used on breached skin.

			Moreover, the definition of non-invasive devices limited to the application on intact skin is not consistent with the MEDDEV 2.4 /1Rev.9 on Medical Device classification, where it is stated that invasive device is a device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body. Moreover, Rule 4 of the MEDDEV guideline includes the category of non-invasive devices which come into contact with injured skin. According to this rule a device can be considered as non-invasive even if coming into contact with an injured skin (not intact), including wound dressing.	
86	king mel, mhra, , United Kingdom	3.8.5. Specific types of medical devices	3.8.5. Specific types of medical devices Page 42 line 19 general comment on Specific Types of Medical Device A particular challenge, which might have been acknowledged in the SCHENIR Preliminary Opinion is the subject of complex combination products involving nanotechnologies - e.g. a combination may include one or more medical devices in addition to an injected "medicinal product". Various combinations of drugs, nanomaterials and activating devices are possible. An example is tumour ablation with heat using the AuroLase Therapy system which is comprised of three components:	SCENIHR partly agrees with the comment. However, it was not within the mandate of SCENIHR to look into the issue of combination products. So, these were not considered in the Opinion. Text is added to indicate the issue of combination products. “Combination products. A specific subgroup may be so-called “combination products”, products consisting of a medical device and containing a medicinal product. Such products need to be evaluated according to the Medical Device Directive and for the medicinal product part advice should be obtained from a medicinal product competent authority or EMA.”

			• near infrared laser source, • interstitial fiber optic probe for delivery of the laser energy to a site near or inside the tumor • AuroShell particles, a near-infrared absorbing, inert material designed to absorb and convert the laser energy into heat. (see http://www.nanospectra.com/clinicians/aurolasetherapy.html for further details) These combination products seem increasingly likely in the future. Guidance on how safety should be evaluated would be useful in order to encourage a harmonized approach in Europe before these products become more commonly used Page 42 Line 21 Wound care materials are mentioned as a specific type of medical device. “Wound care materials” would be better stated as “Dressings for wound care”, Dressings are often considered Devices. Other wound care materials might be considered Medicinal Products; for example products to treat wounds and infection such as anti-septic agents and desloughing agents are considered medicinal products.	
87	king mel, mhra, , United Kingdom	3.8.5. Specific types of medical devices	Page 42 Line 36 – 43 Injectable nanomaterials are mentioned. By stating “injectable nanomaterial” (without further qualification) as an example of a specific type of medical device, the impression is given that classification of injectable	SCENIHR agrees with the comment. The proposed text has been added. “In exceptional circumstances injectable nanomaterials might be classified as Devices rather

			nanomaterials as Devices is a common occurrence. This is misleading as the majority of injectable nanomaterials are classified as medicinal products not medical devices. It is suggested to add the following sentence at the start of the paragraph: "In exceptional circumstances injectable nanomaterials might be classified as Devices rather than Medicinal Products. For injectable nanomaterial, the potential…..." Further discussion of this issue of injectable products being considered Devices: Although, the document makes reference to one injectable nanomaterial containing product classified as a Device (reference to Magforce made on pages 7 and 19 and there may be another such product i.e. Sienna+ from Endomagnetics http://www.endomagnetics.com/?page_id=895), these products are in the minority compared to injectable medical products containing nanomaterials. The following list gives examples of injectable nanopharmaceuticals classified as Medicinal Products rather than Devices (details may be found on the MHRA* or EMA** web-sites concerning authorisation of these medicinal products): Liposomal amphotericin B (an antifungal) for	than Medicinal Products. For injectable nanomaterial, the potential…… " The listing of nanopharmaceuticals is appreciated but not further considered as it is outside the mandate of the Opinion.

			injection or infusion: • Ambisome (PL16807/0001) Authorised 11/09/1998 • Abelcet (PL 14776/0110) Authorised 16/02/2006 • Abelcet (PL 16260/0015) Authorised 16/02/2006 Liposomal Doxorubicin • Caelyx (Doxorubicin) ((EMA licence) EU/1/96/011/001-004) Authorised 21/06/1996 • Myocet (Doxorubicin) (EMA licence) EU/1/00/141/001-002) Authorised 13/07/2000 Liposomal Daunorubicin • Daunoxome (Daunorubicin) PL 27927/0007 Authorised 03/07/2006 Liposomal Cytarabine • Depocyt (cytarabine) (EMA licence) EU/1/01/187/001) Authorised 11 July 2001 Liposomal Morphine • Depodur PL 13621/0040 Authorised 20/04/2006 Liposomal/Lipidic Verteporfin • Visudyne (EMA licence) EU/1/00/140/001 (Liposome/Lipidic verteporfin) Authorised 1127/07/2000 Albumin bound paclitaxel • Abraxane (EMA licence) EU/1/07/428/001-002) Authorised 11/01/2008 Albumin based radiopharmaceutical diagnostic agents	

			• Nanocoll PL 16991/0001 Authorised 15 June 1998 • Nanotop PL 41222/0002 Authorised February 2014 The following parenteral iron products are nano-colloids: • Venofer , Iron Sucrose PL 15240/0001 Authorised 1998 • Cosmofer, Iron Dextran PL 18328/0001 (DK/H/169/1) Authorised 2001 • Ferinject, Ferric Carboxymaltose UK/H/894/0001/DC PL 15240/0002 Authorised 2007 • Monofer, Iron dextran 1000 complex SE/H/734/01/DC PL 18380/0001 Authorised 2010 • Rienso, Ferumoxytol (EMA licence) EMEA/H/C/002215 Authorised 2012 *MHRA web-site (Medicines Information: SPC & PIL): http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs/index.htm **EMA web-site – (Find a medicine): http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124	
88	king mel, mhra, , United Kingdom	3.8.5. Specific types of medical devices	Page 42 Line 36 – 43 Injectable nanomaterials are mentioned. The EMA has produced reflection papers on iron-based nano-colloids, surface coatings on	SCENIHR agrees with the comment. Additional information has been added on page 42 including a reference to the document on the EMA website.

			nanomedicines, liposomal products, and block co-polymer micelles. Whether classified as a device or medicine, it might be expected that the requirements for an injectable nanoparticle would be similar. Therefore, reference to the EMA's reflection papers on injectable nanomedicines would be a helpful guide to include. (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000564.jsp&mid=WC0b01ac05806403e0).	"EMA (London, UK) has published several Guidance documents on injectable nanomedicines (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000564.jsp&mid=WC0b01ac05806403e0)."
89	Dahms Janell, 3M/3M ESPE Dental Products Division, jkdahms@mmm.com, United States	3.8.5. Specific types of medical devices	Lines 28-30"Dental and bone fillers and cements may contain and even consist of free nanoparticles. Mostly cements and dental fillers are cured in situ resulting in a solid mass of (bio)material." Suggested rewording: Uncured dental and bone fillers and cements may contain, and in some cases consist of, free nanoparticles. Cements and dental restoratives are typically cured in situ, resulting in a solid mass of (bio)material. In cases where nanoparticles are surface treated (e.g, the fillers in many dental restoratives), the nanoparticles will be covalently bound into the matrix of the (bio)material, thus limiting bioavailability.	SCENIHR partly agrees with the comment. The text has been modified as follows: "Uncured dental and bone fillers, and cements may contain and even consist of free nanoparticles. Cements and dental fillers are typically cured in situ resulting in a solid mass of (bio)material. During the application of dental materials and also during surface treatment e.g. polishing, nanoparticle exposure may occur."
90	Dahms Janell, 3M/3M ESPE Dental Products	3.8.5. Specific types of medical	Lines 46-47 "The handling of dental materials may also result in respiratory tract exposure to particles (Van Oberdörster et al.	SCENIHR agrees with the comment. Text has been added/modified accordingly.

	Division, jkdahms@mmm.com, United States	devices	2014).” It appears that the citation of Van Oberdörster et al. 2014 should be Van Landuyt et al. 2014. Text should be revised to include points raised in Bogdan et al. 2014.	“Also the handling, e.g. polishing, of dental materials may result in respiratory tract exposure to particles ((Van Landuyt et al., 2012, 2014; Bogdan et al., 2014).
91	Dahms Janell, 3M/3M ESPE Dental Products Division, jkdahms@mmm.com, United States	3.8.5. Specific types of medical devices	Lines 47-48 “Inhalation of various particles was shown to consistently induce local adverse effects in the lung.” This is a broad generalization without cited references or review article to support the statement. Pulmonary effects caused by different nanoparticles vary greatly in type and severity. Adverse effects often occur only at high inhaled concentrations that would be unlikely to occur as a result of exposure to a medical device. Findings from animal studies utilizing alternative dosing techniques such as intratracheal instillation or pharyngeal aspiration are often not consistent with findings from inhalation studies. Also, the text as written is inconsistent with the findings of Smulders et al. (2014), who noted reduced toxicity for embedded vs. pristine nanomaterials. This finding is potentially relevant to dental materials, since grinding or polishing has the potential to produce matrix-coated, embedded, or partially embedded particles (Van Landuyt et al., 2014; Bogdan et al. 2014). We also note that a recent review (Froggett et al. 2014) suggests that grinding, polishing, or	SCENIHR partly agrees with the comment. The intention here is to indicate possible effects on the respiratory system. The adverse effects of particles including nanoparticles has been well established, so a reference was not felt necessary. The issue of toxicity and the changes in (nano)particle composition are discussed elsewhere (section 3.5.1) in the Opinion including the reference (Smulders et al., 2014, Bogdan et al., 2014). Text added to 3.5.1. “Nanoparticles may be generated through abrasive wear or grinding of a material (Frogget et al., 2014). Several scenarios could be identified for nanoparticle release including machining, weathering, washing, contact and incineration (Frogget et al., 2014). Identified debris were particles from matrix alone, matrix particles with the nanomaterial embedded, the nanomaterials themselves or dissolved ionic forms of the added nanomaterial.”

			manipulation of solid nanocomposites in general is most likely to produce particles consisting of embedded or partially embedded nanomaterials, rather than free nanomaterials. Due to copyright restrictions, the following is provided in lieu of document upload: Froggett SJ, et al. (2014). A review and perspective of existing research on the release of nanomaterials from solid nanocomposites. Part. Fibre Toxicol. 11, 17. (doi:10.1186/1743-8977-11-17). Smulders, S, et al. (2014). Toxicity of nanoparticles embedded in paints compared with pristine nanoparticles in mice. Toxicol Sci. Published online June 12.	
92	Stock Gregor, FIDE - Federation of the European Dental Industry, g.stock@fide-online.org, Germany	3.8.5. Specific types of medical devices	In line 33 – 35 the risk for lung exposure to nanoparticles from dental materials is mentioned. However, the probability of occurrence of such an exposure is very low due to the wet environment during use (wear particles will be most probably swallowed with saliva) and due to the use of water spray as state of the art during processing (grinding, polishing).	SCENIHR agrees with the comment. However, this is a matter of the risk assessment and is thus not included in the section 3.8.5 describing medical devices containing nanomaterials.
93	king mel, mhra, , United Kingdom	3.8.6. Conclusions	3.8.6. Conclusions 4. RISK EVALUATION Page 46 Line 6-16 Particle persistence is mentioned but breakdown products are not mentioned in this section. Although the scope of the document is nanomaterials it would be expected that risk assessment	SCENIHR partly agrees with the comment. Page 46 Line 6-16 The focus is on the additional risk aspects because of the use of nanomaterials in medical devices. The evaluation of possible breakdown products of a

			would also take into account the breakdown products of the particle. For example the coating of a coated nanoparticle might dissociate and have effects different to the nanoparticle. Page 47 Table 5 In Table 5 on page 47 MHRA are unsure what is meant by full assessment. Surely a full toxicology assessment should be made for all medical devices regardless of how they are used. This assessment takes into account duration of use, exposure and location of device. If full assessment refers to a full toxicology testing package then MHRA would like to reiterate our earlier point where only those endpoints that are not addressed by already available information require animal testing. Page 47 line 15 to 16 The following is stated "In addition to the estimated potential risk, ultimately also the potential benefit for the patient should be considered in the final benefit risk evaluation". Other than this statement assessment of benefit is not considered in the document. This might be considered an important component of "Risk Evaluation". There seems a divergence in approach between EU and US regulators in this regard. If Magforce's NanoTherm product. is considered: although it was approved (CE marked) for treatment of brain cancers, including glioblastoma in 2010 the company have this year met with FDA (5 May 2014) and have begun enrolling patients	medical device is already part of the evaluation of medical devices itself in which potential leakage of chemicals and breakdown product need to be considered according to ISO 10993-1: 2009. Also breakdown products of coated nanomaterials are then included. Page 47 Table 5 The assessment indicated is the assessment of the nanomaterial used. The assessment of a medical device is dependent on the type of device, duration of contact and the type of tissue contact. Although a risk assessment has to be done for every medical device, this does not automatically means that all toxicology assays have to be performed. This has been clearly stated in the Opinion Page 47 line 15 to 16 For medical devices, the benefit is part of the risk assessment (ISO 14971:2007). A risk-benefit analysis is part of the risk management of a medical device. Indeed there are differences in the regulatory approach of medical devices between the EU and the USA. The competent authorities control the notified bodies, and can when indicated ask for a second view of the submitted data. This is a regulatory issue that is outside the mandate of the SCENIHR.

			for a further trial. It seems that evidence required to support risk/benefit assessment is greater in the US. Why was data submitted in support of the product considered acceptable in the EU but not in the US? As this product was CE marked by a notified body it is unlikely that any Competent Authority has access to the data. This raises questions on transparency in the regulation of Medical Devices and its appropriateness for high risk products such as this, on the borderline with Medicinal Products..If notified bodies are CE marking these products then EU Guidance on the level of data required to support risk/benefit should perhaps be provided.	
94	king mel, mhra, , United Kingdom	3.8.6. Conclusions	Although allowing products onto the market with perhaps a limited amount of clinical evidence supports innovation, the lack data may hinder clinicians in making decisions with regard to treatment, especially where there are other competing treatment options, to the detriment of patient care. There are ways of addressing this via adaptive licensing and early access to medicines schemes (see MHRA Early Access to Medicines Scheme http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm). The following press releases confirm the marketing in the EU in 2010 and the FDA	This is a regulatory issue that is outside the mandate of the SCENIHR.

			positions on further data being required to support its use in the US. http://www.clinica.co.uk/marketsector/other/INTERVIEW-MagForce-turns-the-heat-up-on-NanoTherm-cancer-therapy-push-353329 “NanoTherm’s CE mark in 2010 was for treatment of brain cancers, including glioblastoma, and the clinical evidence from a Phase II, 59-patient study of the therapy was strong, believes Dr Lipps. “There were patients with recurring glioblastoma who essentially had around 13 additional months of life [after being treated with NanoTherm] versus historic controls, which had around six additional months – the company really had a very good product.” http://inpublic.globenewswire.com/2014/05/05/MagForce+AG+and+MagForce+USA+Inc+Announce+FDA+Pre+IDE+Meeting+HUG1782465.html Berlin, Germany and Nevada, USA, May 5, 2014 - MagForce AG (Frankfurt, Entry Standard, XETRA: MF6), a leading medical device company in the field of nanomedicine focused on oncology, together with its subsidiary MagForce USA, Inc. are pleased to report that an in-person meeting was held with the U.S. Food and Drug Administration's (FDA) Center for Devices and Radiological Health to discuss FDA's response to MagForce's NanoTherm® Therapy Pre-Submission of late December, 2013.	

			"We received very constructive feedback on our submission and have a better understanding of the issues and process for registration of NanoTherm® therapy in the USA. MagForce USA, Inc. will lead with the treatment of recurrent Glioblastoma in concert with MagForce AG's post marketing clinical trial in Germany, which has already begun enrolling patients. We are confident that MagForce AG's extensive pre-clinical and clinical studies will provide the background for a timely submission of an Investigational Device Exemption (IDE) for the application of NanoTherm® Therapy," commented Ben J. Lipps, CEO of MagForce AG and MagForce USA.	
95	Berzanskis Laurel, Health Care Without Harm Europe, laurel.berzanskis@hcwh.org, Belgium	4. RISK EVALUATION	Page 45, lines 2-3 - In this context it is then especially important to define equivalence. In our Opinion equivalence is near impossible to achieve (see earlier comments on effect of shape) and the particles studied should be exactly the same. Page 45, lines 5-8 - Size and shape of a chemical in its soluble form can also be important, as this may determine if and how the chemical fits into receptors, etc. Additionally in its Opinion on the risk assessment of nanotechnologies the European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR 2009, p52) stated that: "For (partially) soluble nanomaterials the toxicity	SCENIHR partly agrees with the comment. Page 45, lines 2-3 The nanomaterials have been processed and may be altered during the processing. The statement wants to raise awareness on the issue, that this should be taken into consideration. Page 45, lines 5-8 No comment. The inclusion of larger structures in the definition is not an issue within the mandate of the current Opinion. Page 45, lines 10-12

			may be governed at least in part by the soluble species/fraction released from the nanomaterial. For low solubility or a slow release, the particulate nature of the substance may be relevant with regard to potential tissue distribution and local release of toxic species which should then be considered in the risk assessment of such nanomaterials." Partially soluble nanomaterials may have very different bioavailability, biokinetics and biopersistence compared to ions and soluble forms of the same chemical composition. Even wholly soluble nanomaterials made of non-metal substances (eg micelles, nano-liposomes and nano-encapsulated active ingredients) possess novel properties and biological behaviours compared to larger forms of the same substances, and therefore must be included within the definition of 'nanoparticles' and subject to nanotechnology-specific risk assessment and exposure metrics. See attached Scenihr report on risk assessment of nanotechnologies; Page 45, lines 10-12 - The unique parameters that will identify a nanoform of a substance include (but may not necessarily be limited to) size, the number-based particle size distribution (PSD) and the shape of the nanomaterial. Another important aspect when considering description of	The section deals with the characterisation of the released nanomaterials. The determination of other characteristics includes possible surface composition of a nanomaterial (ISO 13014:2012). Surface characterisation has been added as an example of other characteristics. "• Other characteristics dependent on the nanomaterial used like surface chemistry/composition (see also ISO TR 13014:2012)"

			nanomaterials is surface treatment. This is often applied to prevent nanomaterials from aggregating/ agglomerating and to preserve and/or enhance their unique nanoform properties. Surface treatment should be recorded as a standard measure when considering toxicity testing.	
96	Berzanskis Laurel, Health Care Without Harm Europe, laurel.berzanskis@hcwh.org, Belgium	4. RISK EVALUATION	Page 45, line 13-16 - We disagree with this statement. Nano-structured aggregates may be larger than 100nm – or even larger than 300nm. In many instances aggregates will have close to the same surface area as the nanoparticles they are made from and will have 'nooks and crannies' on their surface structure that are nano-sized. Where toxicity is driven by surface characteristics, the toxic properties of aggregated nanoparticles may be very similar to that of the primary nanoparticles that compose them. In other instances, nano-structured aggregates have resulted in greater damage than that associated with the primary nanoparticles. In an inhalation study using mice Shvedova et al. (2005) found that aggregates of single walled carbon nanotubes were the focal point of granulomatous inflammation. In their study of the biokinetics of quantum dots, Chen et al. (2008) found that aggregates of silica-coated cadmium quantum dots that had bound with proteins had the greatest biopersistence and therefore presented the	SCENIHR disagrees with the comment. Especially for aggregates with a firm bonding disaggregation is very difficult and the total surface area is less when compared to single nanoparticle dispersion. For agglomerates with a loose bonding dis-agglomeration into single nanoparticles is more likely depending on the forces working on the nanomaterial. This text is not about the potential toxicity but on the nanospecific properties that might be present for a specific nanomaterial used in a medical device. For clarification the text has been slightly modified. "• Ability to agglomerate and dis-agglomerate. The ability for particles to combine and dissociate is also a factor that affects particle size. The larger the particle size in biological media **the less likely will** be the retention of the surface active properties that are associated with nanoparticles."

			most serious potential future risk should their coatings degrade. Nonetheless, agglomeration does not necessarily reduce particle toxicity. For example Muller et al. (2005) found that 2 months after intratracheal installation of multi-walled carbon nanotubes in rats, pulmonary lesions were caused by the accumulation of large carbon nanotube agglomerates in the airways. It is still largely unknown to what extent aggregates and agglomerates will break down into smaller particles in our bodies, e.g. after inhalation. Researchers routinely use surfactants to 'debundle' single and multi-walled carbon nanotube samples for physicochemical investigation (Blackburn et al. 2006, Lisunova et al. 2006). Biological fluids, e.g. the lung's epithelial lining fluid which contains both surfactants and proteins, may similarly promote de-agglomeration (Maynard 2007, Oberdörster et al. 2007) or even break up of aggregates (Donaldson et al. 2006) into smaller clumps or even into the primary nanoparticles or fibres. Attached articles: Maynard A. 2007. Is engineered nanomaterial exposure a myth? Available at: http://www.safenano.org/MaynardNanoMyth.aspx Shvedova A, Kisin E, Merecr R, Murray A, Johnson V, Potaponvich A, Tyurina Y, Gorelik O, Arepalli S, Schwegler-Berry D, Hubbs A, Antonini J, Evans D, Ku B, Ramsey	

			D, Maynard A, Kagan V, Castranova V, Baron P. 2005. Unusual inflammatory and fibrogenic pulmonary responses to single-walled carbon nanotubes in mice. Am J Physiol: Lung, cell and mol physiol 289:698-708. Chen Z, Chen H, Meng H, Xing G, Gao X, Sun B, Shi X, Yuan H, Zhang C, Liu R, Zhao F, Zhao Y, Fang X. 2008. Bio-distribution and metabolic paths of silica coated CdSeS quantum dots. Toxicol Appl Pharmacol 230:364–371 Muller J, Huaux F, Moreau N, Misson P, Heilier J-F, Delos M, Arras M, Fonseca A, Nagy J, Lison D. 2005. Respiratory toxicity of multi-walled carbon nanotubes. Toxicol Appl Pharmacol 207(3):221–31. Lisunova M, Lebovka N, Melezhyk O, Boiko Y. 2006. Stability of the aqueous suspensions of nanotubes in the presence of non-ionic surfactant. J Colloid Interface Sci 299(2):740-746. Blackburn J, Engtrakul C, McDonald T, Dillon A, Heben M. 2006. Effects of surfactant and boron doping on the BWF feature in the Raman spectrum of single-walled carbon nanotubes aqueous disprsions. J Phys Chem B 110(50):25551-25558. Oberdörster G, Stone V, Donaldson K. 2007. Toxicology of nanoparticles: An historical perspective. Nanotoxicology 1(1):2-25. Donaldson K, Aitken R, Tran L, Stone V, Duffin R, Forrest G, Alexander A. 2006.	

			Carbon Nanotubes: A Review of Their Properties in Relation to Pulmonary Toxicology and Workplace Safety. Toxicol Sci 92(1), 5–22	
97	Dahms Janell, 3M/3M ESPE Dental Products Division, jkdahms@mmm.com, United States	4. RISK EVALUATION	Lines 27-31 "If there is reliable evidence that the nanomaterials are embodied in the device or so well fixed that they will be retained in the device during insertion, period of use and removal then, provided particles are not released as a consequence of wear, no further specific risk assessment regarding the nanoparticle component is required." What would constitute "reliable evidence" in this case? Considering the lack of good methods for measuring nanomaterials in biological samples, this would seem to be very difficult to demonstrate.	SCENIHR agrees with the comment that "reliable evidence" is difficult to ascertain. The text has been modified. "If there is **substantial** evidence that the nanomaterials…"
98	Dahms Janell, 3M/3M ESPE Dental Products Division, jkdahms@mmm.com, United States	4. RISK EVALUATION	Lines 44-45 "In addition, local effects in the lung itself need to be considered as most if not all particles induce lung inflammation." Particulate-induced lung inflammation is a concentration-related phenomenon and varies greatly in severity for different nanomaterials.	SCENIHR agrees with the comment that lung inflammation is a dose dependent phenomenon. The issue is that awareness is raised for the possibility that lung inflammation can be induced.
99	Dahms Janell, 3M/3M ESPE Dental Products Division,	4. RISK EVALUATION	Lines 13-15 "The estimated risk may be compared to the risk from the use of comparable devices not incorporating nanomaterials, and assessed according to	SCENIHR partly agrees with the comment. However, concurrent testing may not be possible or advisable if the nano-component is added as an improvement. In order to avoid unnecessary testing data from

	jkdahms@mmm.com, United States		ISO 14971." Where possible, conducting side-by-side testing of a device with and without the added nanomaterial within the ISO 10993 framework would seem be the most effective way to assess the potential hazard associated with the nanomaterial, especially if analytical limitations make it difficult or impossible to measure nanomaterial release/exposure from the device.	older/previous studies might be used for comparison.
100	Dahms Jaell, 3M/3M ESPE Dental Products Division, jkdahms@mmm.com, United States	4. RISK EVALUATION	Lines 1-4 "If even a small release of particles is considered possible, then evaluation of the physicochemical properties of the released particles is necessary. It is essential that the particles studied in assays for the risk assessment are equivalent, in terms of both physical and chemical properties, as those that may be released in situ." In most cases, the particles that are released from solid nanocomposite products have been shown to consist primarily of the product matrix, not the nanoparticles that were added to the product (reviewed in Frogget et al. 2014). Characterizing the physicochemical properties of the mixture of released particles, especially if only a few of them are the intentionally added nanoparticles, could be extremely difficult, if not impossible at this time. Due to copyright restrictions, the following is provided in lieu of document upload:	SCENIHR agrees with the comment. This aspect has been discussed in section 3.5.1 . including Frogget et al., 2014. For clarification the text of 3.5.1 is repeated here. "Several scenarios could be identified for nanoparticle release including machining, weathering, washing, contact and incineration (Frogget et al., 2014). Identified debris were particles from matrix alone, matrix particles with the nanomaterial embedded, the nanomaterials themselves or dissolved ionic forms of the added nanomaterial."

			Froggett SJ, et al. (2014). A review and perspective of existing research on the release of nanomaterials from solid nanocomposites. Part. Fibre Toxicol. 11, 17. (doi:10.1186/1743-8977-11-17).	
101	Dahms Janell, 3M/3M ESPE Dental Products Division, jkdahms@mmm.com, United States	4. RISK EVALUATION	Lines 41-42 "Significant uptake of particles from the lung into the systemic circulation is more likely than from other external location sites." Translocation of nanoparticles from the lungs into the systemic circulation has been shown to be quantitatively insignificant (< 1%) in most studies in which it has been measured. Engineered nanomaterial aerosols tend to from agglomerates which do not disagglomerate in the lung and do not become systemically available (reviewed in Landsiedel et al. 2012). Due to copyright restrictions, the following is provided in lieu of document upload: Landsiedel R, et al. (2012). Toxico-/biokinetics of nanomaterials. Arch. Toxicol. 86, 1021-1060.	SCENIHR partly agrees with the comment. Even when the uptake is low as percentage of the dose expressed in mass, this still can be a considerable amount of particles based on number. This is even more important when non-degrading particles are used with the possibility for prolonged persistence. The text has been adapted. The word Significant is deleted.
102	GARNY Veronique, Cefic, vga@cefic.be, Belgium	5. SUMMARY AND CONCLUSIONS	 CEFIC comments.pdf	Please see the answers formulated in the document attached.  Answers to CEFIC comments Final.docx

103	Dahms Janell, 3M/3M ESPE Dental Products Division, jkdahms@mmm.com, United States	5. SUMMARY AND CONCLUSIONS	Line 14-16 "If as a result of these studies, it is concluded that even under realistic worst-case use conditions particle release will be very low, no further consideration of the risk should be required. Further considerations are needed when a substantial release is noted." What is considered "very low" and "substantial" in this case? Is there a threshold below which the risk can be considered negligible for any nanomaterial?	SCENIHR agrees with the comment. Very low and substantial are indeed difficult to quantify. This terminology was used to give an indication of amount of nanoparticles released. There is no threshold available at the moment at which the risk can be considered negligible. A comparison with a toxicity study with the free nanomaterial might give an indication for a non-toxic dose/exposure. The text has been adapted to address the issue of significant. Terminology of the main text is copied here. "If as a result of these studies, it is concluded that even under realistic worst case use conditions particle release does not occur or will be negligible the further evaluation may be limited mainly to investigate local reactions.. When significant exposure is expected due to nanoparticle release further evaluation of the risks is necessary. The definition of what is considered a negligible or significant amount is dependent on the type of nanomaterial (e.g. use of a nanomaterial with known/suspected high or low toxicity)."
104	Sanak Aleksandra, Council of European Dentists (CED) ,	5. SUMMARY AND CONCLUSIONS	Lines 44 - 46: The CED shares SCENIHR's Opinion that medical devices not containing nanomaterials can generate nanoparticles as a result of wear-and-tear. The approaches	SCENIHR agrees with the comment.

	ced@eudental.eu, Belgium		indicated in the preliminary Opinion may also be applicable for such wear-and-tear generated nanoparticles.	
105	Sanak Aleksandra, Council of European Dentists (CED), ced@eudental.eu, Belgium	5. SUMMARY AND CONCLUSIONS	Lines 33 - 37: The risk assessment should be performed on a case-by-case basis, for each specific medical device containing nanomaterials.	SCENIHR agrees with the comment. For all medical devices a risk assessment has to be performed to determine whether the use of the medical device has an acceptable risk.
106	Dahms Janell, 3M/3M ESPE Dental Products Division, jkdahms@mmm.com, United States	8. REFERENCES	An additional reference to consider for inclusion into the Opinion: Moreno-Hom M, et al. (2014). Granular biodurable nanomaterials: No convincing evidence for systemic toxicity. Posted online on September 26, 2014. (doi:10.3109/10408444.2014.938802)	SCENIHR partly agrees with the comment. Although this is a good overview of toxicity of granular biodurable nanomaterials, the paper is outside the scope of the Opinion. The paper reviews outcomes of granular large sized particles with nanoparticles of the same chemical composition. The paper is dealing with granular biodurable particles without known specific toxicity. Most reviewed papers do not show a novel nano-specific toxicity as stated by the authors. “There was no valid indication that GPB nanomaterials possess novel toxicological hazard properties”. Toxicities are similar for nano-and larger sized particles. The Guidance addresses how to evaluate potential toxicity of nanomaterials. Text in section 3.7.1 was added to reflect that there may be no novel nano-specific hazards. “However, for granular biodurable particles without known specific toxicity (GBP) no valid indication was

				observed that GBP nanomaterials possess novel toxicological hazard properties (as reviewed by Moreno-Horn and Gebel 2014)."
107	Stock Gregor, FIDE - Federation of the European Dental Industry, g.stock@fide-online.org, Germany	8. REFERENCES	Additional References: Bogdan, A., Buckett, M.I., Japuntich D.A. (2014). Nano-Sized Aerosol Classification, Collection and Analysis - Method Development Using Dental Composite Materials. J Occupational and Environmental Hygiene 41, 415-426 Heumann, T., Dermann, K. (1979) Zur Frage der Existenz eines Ouerdrucks in mit Flüssigkeit gefüllten Kapillaren. Teil I. Z Metallk. 70, 281-285 Heumann, T., Dermann, K. (1979) Zur Frage der Existenz eines Ouerdrucks in mit Flüssigkeit gefüllten Kapillaren. Teil II. Z Metallk. 70, 286-292 Smulders, S., Luyts, K., Brabants, G., Van Landuyt, K., Kirschhock, C., Smolders, E., Golanski, L., Vanoirbeek, J., Hoet P.H.M. (2014). Toxicity of Nanoparticles Embedded in Paints Compared with Pristine Nanoparticles in Mice. TOXICOLOGICAL SCIENCES Advance Access publication June 13, 2014	The following reference were cited and included. Bogdan et al., 2014 Smulders et al., 2014.
108	Prina-Mello Adriele, Trinity College Dublin & ETP Nanomedicine, prinamea@tcd.ie,	8. REFERENCES	To be included into the references Online scientific literature and weblink EGE 2007, N & ET Working Group. Report on nanotechnology to the medical devices expert group findings and Recommendations.	It is not the intention of the Opinion to discuss all kinds of nanomaterials in the Opinion. Only aspects related to medical devices and potential hazards/risks are discussed. Most provided references are by itself interesting, but do not

	Ireland		2007. Available: http://ec.europa.eu/enterprise/medical_devices/net/entr-2007-net-wg-report-nanofinal.pdf European Medicines Agency. European Medicines Agency: reflection paper on nanotechnology-based medicinal products for human use (EMEA/CHMP/70769/2006) London: European Medicines Agency; 2006. Endomagnetics: website http://www.endomagnetics.com/ (last accessed 2.10.14). ETP-N White paper titled: NANOMEDICINE 2020 Contribution of Nanomedicine to Horizon 2020 (2013). available online at http://www.etp-nanomedicine.eu/public/press-documents/publications/etpn-publications/etpn-white-paper-H2020. (Available online at http://www.etp-nanomedicine.eu/public/press-documents/publications/etpn-publications/etpn-white-paper-H2020; last accessed 2.10.14). Linsinger et al. (2012) Accreditation of Reference Material Producers: The Example of IRMM's Reference Materials Unit. Available online at JRC portal (http://publications.jrc.ec.europa.eu/repository/) (last accessed 2.10.14). ITS NANO ((INTELLIGENT TESTING STRATEGY FOR ENGINEERED NANOMATERIALS) final report	contain specific issues dealing with medical devices. Cited and included in the Opinion. EMA document on IV iron nanomaterials. EMA (2013) Reflection paper on the data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product. EMA/CHMP/SWP/620008/2012. EMA, London, UK. Christ et al., 2013. Linsinger et al., 2012.

			(http://cordis.europa.eu/result/rcn/144082_en.html) (last accessed 2.10.14). Rip-ON2 document (REACH) available online http://ec.europa.eu/environment/chemicals/nanotech/pdf/report_ripon2.pdf (last accessed 2.10.14). Peer review Scientific literature Crist, R.M., Grossman, J.H., Patri, A.K., Stern, S.T., Dobrovolskaia, M.A., Adiseshaiah, P.P., Clogston, J.D., McNeil, S.E., Common pitfalls in nanotechnology: Lessons learned from NCI's Nanotechnology Characterization Laboratory, (2013) Integrative Biology (United Kingdom), 5 (1), pp. 66-73. Etheridge ML, Campbell SA, Erdman AG, Haynes CL, Wolf SM, McCullough J. The big picture on nanomedicine: the state of investigational and approved nanomedicine products. Nanomedicine 9:1, 1-14, 2013. Prina-Mello A, Diao Z, Coey JM., Internalization of ferromagnetic nanowires by different living cells. J Nanobiotechnology. 5;4:9. (2006) (available online at http://www.jnanobiotechnology.com/content/4/1/9; last checked 2.10.14) Poland CA, Byrne F, Cho WS, Prina-Mello A, Murphy FA, Davies GL, Coey JM, Gounko Y, Duffin R, Volkov Y, Donaldson K., Length-dependent pathogenic effects of nickel nanowires in the lungs and the peritoneal cavity. Nanotoxicology. 6:899-911. (2012) Roebben G., Rasmussen K., Kestens V., Linsinger T.P.J., Rauscher H., Emons H., Stamm H.,	

			Reference materialos and representative test materials: the nanotechnology case, J. Nanoparticle Research 2013. 15:1455. Santos-Martínez MJ, Prina-Mello A, Medina C, Radomski MW. Analysis of platelet function: role of microfluidics and nanodevices. Analyst. 21;136(24):5120-6. (2011) Samuel SP, Jain N, O'Dowd F, Paul T, Kashanin D, Gerard VA, Gun'ko YK, Prina-Mello A, Volkov Y. Multifactorial determinants that govern nanoparticle uptake by human endothelial cells under flow. Int J Nanomedicine. 7:2943-56. (2012) Verma NK, Conroy J, Lyons PE, Coleman J, O'Sullivan MP, Kornfeld H, Kelleher D, Volkov Y. Autophagy induction by silver nanowires: a new aspect in the biocompatibility assessment of nanocomposite thin films. Toxicology and Applied Pharmacology, 264:3, 451-461, (2012).	

Name of individual/organisation	Comment	SCENIHRs Response
Comment received via email		
Representation permamanente de la France aupres de l'Union Europeenne, le Conseiller pour la Sante.	French contribution.pdf unofficial translation of French contirbutior	Please read the answers included in the document attached. Answers to French comments Final.docx