SCENIHR Opinion on Nanomaterials in Medical Devices.

Answers to comments ETPN.

General comments.
SCENIHR agrees with the general comment on the Preliminary Opinion. Especially when considering the grey area between medical devices and medicines. It is indeed for the regulators to address these issues.

Page 4
Definition nanomaterials.
SCENIHR agrees with the comments made. However, the mandate for the guidance is only on medical devices, so implications for medicinal products are not considered. 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).
Whether there will be a common definition for both the medicinal products area and medical devices is outside the mandate of SCENIHR.

However, it should be realised that it is possible to apply the text as mentioned in the Opinion also for particles in a medical device with a size larger than 100 nm.

Text has been added to the Abstract, and summary and Conclusions section.
"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."

Page 4, line 14 – 25 (and thereafter)
Other examples. SCENIHR agrees with the comment. However, within the abstract the most common application are mentioned and it is not meant to be an exhaustive list of all the possibilities. The issue of degradation is discussed in section 3.5 on exposure.

Page 4 line 23 (and thereafter)
Wear and tear.ISCENIHR agrees with the comment that recent scientific progress in nanotechnology has now also been extended to a more detailed evaluation of wear and tear particles. The techniques mentioned in Table 1 might also be used for the characterization of such "debris" particles.

Section 1 Background
Page 7, Line 17-18
Section 2 Terms of reference
The background and terms of references is text provided by the European Commission when formulating the questions for the SCENIHR mandate. As such these cannot be changed by SCENIHR.

SECTION 3: GUIDANCE ON SAFETY EVALUATION OF NANOMATERIALS USED IN MEDICAL DEVICES
Page 10, line 33---35.
SCENIHR provided information as currently available. The SCENIHR Opinion 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 or the classification of such products. It is for the regulators to decide on such borderline products.

Page 10, Line 38-40
The SCENIHR Opinion 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 or the classification of such products. It is for the regulators to decide on such borderline products.

Page 13
Physical chemical characterization. SCENIHR agrees with the comment. Characterization is warranted also for local release. This issue is discussed in detail in section 3.5.1 Exposure. For further clarification text has been added on page 21 at the end of section 3.5.1.

"In all circumstances in which there is a possibility for the generation and release of (nano)particles a careful characterization of the particles is necessary according to the methods described in section 3.3.1 and 3.3.2."

Page 14 line 31
SCENIHR agrees with the comment. However, SCENIHR cannot answer the question what the criteria should be for similarity. Justification should be provided. It is to the regulators to decide on such an issue.

Page 15 Table 1
Chemical composition. Both the EELS and EDX techniques are indicated on page 16 as identification techniques within electron microscopy uses.
Particle size. SCENIHR agrees with the comment. NTA and STM were already included in Table 2 and are now added to Table 1 as well.
Physical form and morphology. The list is extensive but not exhaustive. XPS is indicated under surface chemistry as it is a method to measure elemental composition rather than size.

Page 16 line 10-25
SCENIHR agrees with the comment. NTA has been added to the text on page 16 line 10-25.

Page 16 line 22
SCENIHR agrees with the comment. NTA has been added to the text on page 16 line 22.

Page 17 line 6-9
SCENIHR agrees with the comment. Example is deleted.

Page 17 line 6
SCENIHR agrees with the comment. However, reproducibility is an issue for all methods used. The report of Linsinger et al., 2012 provides an excellent overview of the issues regarding measurement techniques.

Page 17 line 10-18
Crist et al., 2013 is included in the Opinion.

Page 18 line 17
Nanoneedles. Needles are indicated in line 22.

Page 18 line 31
The catheter is included as example in the section of "external communicating invasive device" on page 18.

Page 19 line 13
Another product. The example of a specific product was removed. So, an additional example is not needed. The following text was added citing the paper of Etheridge et al., 2013.

"Etheridge et al., (2013) concluded the following on the use of nanomaterials in medical devices. "The device categories included in vitro testing, in vivo imaging, in vivo device coatings, bone substitutes, dental, medical dressings/textiles, cancer treatment, surgical devices, drug delivery, tissue engineering, and other. In vitro testing and in vivo imaging were the most prominent categories, followed by in vivo device coatings and bone substitutes."

Page 20 section 3.5, general comment and opinion
SCENIHR thanks ETPN for its comments: it described exactly what the content of the Opinion is. The Opinion raises awareness on many issues considered important for the safety evaluation of nanomaterials including aspects of, for example, assay interference and oxidative stress, which is considered in section 3.7. So, the basic principles on nanomaterial testing are as far as available considered in the Opinion. As medical devices are evaluated according to ISO 10993 series this was used as starting point for the safety evaluation of medical devices including nanomaterials.

Page 20 section 3.8, general comment and opinion
General comments
SCENIHR thanks ETPN for its comments. The risk for a nanomaterial used in a medical device is considered from the testing of medical devices. For the nanomaterial component this is mainly associated with the potential for the release of free nanoparticles. So, this was used as starting point in the risk assessment. The change that a nanomaterial would be released as pristine nanomaterials is highly unlikely. So, although the hazards of the pristine nanomaterial can be helpful in the risk assessment, the risk assessment is especially driven by the exposure possibilities as described in section 3.5.
Genotoxicity testing
SCENIHR agrees with the comment. SCENIHR followed here the common testing of medical devices. Indeed physical properties and chronic inflammation may also lead to tumor development as has been demonstrated for particles and HARN in the lung. The text has been modified based on the comments of ETPN and other comments. See section 3.7.3. The introduction text to the genotoxicty testing paragraphs now reads as follows:

"ISO 10993-1 indicates considerations for identifying when the potential for genotoxicity is a relevant hazard. In general the testing for genotoxicity is not necessary for medical devices, and components thereof, made only from non-genotoxic materials. This rule might also apply for nanomaterials. However, if the genotoxicity of the ingredients including nanomaterials is unknown genotoxicity testing is necessary. ISO 10993–3:2003 describes tests for genotoxicity (carcinogenicity and reproductive toxicology). A recent review on genotoxicity testing concluded that genotoxicity testing should also consider other potential toxic effects in the assays (Magdolenova et al., 2014). "Many studies, both in vitro and in vivo, show positive effects most likely due to the use of concentrations that are not relevant to possible environmental exposure. In many studies a demonstration of genotoxicity simply reflects cytotoxicity, as excessively high concentrations are used. Thus, cytotoxicity should be an integral part of genotoxicity testing to avoid false-positive results" (Magdolenova et al., 2014).

It should be noted that for all genotoxicity assays it is important to establish exposure of the target cells and/or organs to the nanomaterials tested.

It should be noted that besides direct genotoxicity also other mechanisms of toxicity may result in DNA damage and induce indirectly genotoxicity, notably chronic inflammation (Kundu and Surh 2008. Donaldson et al., 2011)."

Cancerogenicity should be considered as an endpoint for some nanomaterials.
Although carcinogenicity indeed cannot be excluded, SCENIHR follows the ISO-10993-1 considerations, in which carcinogenicity is considered based on the type of medical device, type of (organ) exposure and time of exposure. So, the hazard categorization as proposed by the ETPN comments is included in the ISO-10993-1 considerations for testing and risk assessment of medical devices.

Relevance for nanoparticles produced from wear from non-nanotechnological medical devices.
SCENIHR disagrees with this comment. The risk of nanomaterials when used in a medical device is mainly associated with the release of these nanoparticles. So, any other release of particles that are in the nanosized range would pose similar risks as the release of nanomaterials incorporated in a medical device. The Opinion indicates that a similar approach can be made to identify/characterize such debris particles as the tests used for nanomaterials.
The Opinion does not indicate that the protocols can be used to detect the potential release or occurrence of particulate debris. However, when it is found that such a debris is generated it may be evaluated for its risk similar to nanomaterials used in medical devices.

Page 24 lines 6-7.
SCENIHR agrees with the comment. The text has been adapted by indicating that also other forms of release (i.e. ions) might be detected, depending on the medical devices used (metal or polymer implants).

Page 25 lines 22-37.
SCENIHR agrees that the example of gold nanoparticles on toxicokinetics and organ distribution is not representative for a medical device, but this was also not intended for that purpose. It is presented in the introduction to the toxicokinetics section as an example on how important the study of nanoparticles toxicokinetic and biodistribution is.

Page 27 lines 28-30.
For the answer to this comment: see comment above.

Page 29 lines section 3.6.5.
The comment on "ineraction-pathway".
The text has been adapted to indicate the importance of uptake of nanoparticles by organs of the phagocyte mononuclear system (MPS).
In general, after systemic availability the clearance of the nanoparticles from the blood is into the organs of the MPS mainly liver and spleen. So, when release of nanomaterials is likely, the possibilities for translocation and uptake/persistence in organs rich in phagocytic cells (e.g. liver, spleen, bone marrow) should be considered.

Page 29 lines27-39.
Issue of high throughput screening.
SCENIHR agrees with the comment. Indications for the value of this approach is indicated in the Opinion section 3.7.1. SCENIHR supports the development of standards for nanosafety evaluation. However, so far a limited number of standards (2 or 3) have been published by ISO TC 229 nanotechnologies (see ISO website). Most of the documents published by ISO TC 229 have either technical reports (TR) or technical specifications (TS) status. These documents are very useful for the

understanding of the potential problems associated with nanomaterial safety evaluation but do not give guidance or standardized assays.

Page 30-31 section 3.7.2.
SCENIHR agrees with comment that the section 3.7.2 is not specifically dedicated to medical devices. It is dedicated to pitfalls in the testing of nanomaterials/particles. It can be foreseen that some of the safety testing of the nanomaterials used for the manufacturing of medical devices will be done on the nanomaterials themselves rather than on the medical device incorporating the nanomaterials. Therefore, this section was included to specifically raise the awareness on the issues mentioned.

Page 31 lines 3-7.
SCENIHR disagrees with the comment for page 31. This belongs to section 3.7.2 that addresses possible pitfalls in testing of nanomaterials. The example mentioned in the comment is the activity of autophagosomes induced by nanowires as a relatively new nanomaterial toxicity activity. However, the comment and the reference are valid. Text has been added to section 3.7.1 Introduction.

Page 31 lines 29-34.
SCENIHR thanks ETPN for the comment. However, the statement on pa31 lines 29-34 only gives information on how to prepare test samples from medical devices with the addition that also the nanomaterials themselves maybe used in the assays.

Page 32 lines 19-26.
The ACUTE –Tox project is mentioned as an example for the development of toxicological testing. It is the intention to make the reader aware of ongoing activities In the area of alternative testing methods. Such methods might also be applied to medical devices and nanomaterials after proven applicability and/or evaluation/validation. ECVAM has been added to the text.

Page 33 lines 21-27.
As indicated above a categorization of nanomaterials or medical devices is not the focus of the mandate for this opinion. For all medical devices a proper risk assessment has to be performed (for which ISO 10993-1 and 14971 give guidance). The information needed for the risk assessment of a medical device depends on the type and application of the medical device.

Page 34 and 35 Genotoxicity sections.
See answers as presented above. Page 20 section 3.8.

Page 36 lines 11-19.
Haemocompatibility issue. The haemocompatibility assays follow the tests described in ISO 10993-4 for the evaluation of medical devices. As indeed for nanomaterials also other tests may be needed; the example mentioned in the comment is added to the text.
"In addition, new technique (e.g. microfluidics) maybe needed to evaluate the interaction of (nano)particles with endothelial cells or the vasculature (Santos-Martinez et al., 2011, Samuel et al., 2012)."

Page 36-37 line 30 onwards.
SCENIHR agrees with the comment on the oral studies. However, it should be realized that for most chemicals toxicity is indeed evaluated by oral studies and to a lesser extent by inhalation studies. The issue of toxicity evaluation is based on the fact that systemic toxicity can occur after a chemical (nanoparticle) becomes systemically available. So, the information needs to be considered and, even when this is difficult, extrapolated to the use and application site of a medical device. When new

studies are designed one might consider using the route of exposure as it occurring in a medical device application.
Section 3.7 follows the outline as is present in the ISO 10993 series for the biological evaluation of medical devices.

Page 40 lines 3-7.
SCENIHR disagrees with the comment that the Rip-ON2 report might be helpful. In the Rip-ON2 report also the OECD guidelines are cited as well as a number of (ongoing) EU projects. Rip-ON2 contains advice on possible changes in the OECD guidelines and REACH requirements. It is not yet certain how and if the Rip-ON2 advice will be included in the various guidelines/requirements.

Page 43 Risk evaluation sections
Page 44 line 3-15
SCENIHR agrees with the comment. Indeed ISO 10993 does not describe how to demonstrate the lack of release and absorption of nanomaterials. It is, however, an important issue within the risk assessment procedure. In general, if an issue cannot be demonstrated via testing, in the risk assessment a worst-case scenario is assumed. In the case of nanomaterials in a medical device this would mean that it is assumed that 100% of the nanomaterial will be released. As this is most likely not the case, some efforts should be made to estimate the release of the nanomaterial from the medical device in the actual conditions of use.

Page 44 Figure 2 and text description
SCENIHR disagrees with the comment on the conceptual development of the risk evaluation section. The comment does not provide information why the conceptual approach as used by SCENIHR would be inaccurate. Figure 2 is added to give a visual presentation of the evaluation process.

Page 45 lines 1-26.
SCENIHR partly agrees with the comment. The text has been adapted. The text reflects the issue of particle release independent of its shape and/or origin (nanoparticle release or debris generated by wear).

"When there can be a release of nano-sized material in an amount sufficient to raise concern or when such an amount is unknown, then evaluation of the physicochemical properties of the released particles is necessary."

Page 45 from line 28 and thereafter.
SCENIHR partly agrees with the comment. As it is unknown what the size (and shape) of the released material is, the term "particle" was chosen. The released particles can be either in the nanosized range or not.

Page 33 lines 21-27.
SCENIHR agrees with the comment. However, for medical devices safety evaluation ISO 10993-1 has to be followed. So, systemic toxicity may not be needed for all medical devices. The text in the Opinion indicates when the evaluation should be done using assays for systemic toxicity (i.e. when there is exposure of internal organs).
A discussion on the regulatory acceptance of a medical device is not in the mandate of SCENIHR. This is to the regulators to decide.

Page 47 last sentence lines 15-16.
SCENIHR disagrees with the comment. The safety evaluation is based on the determination of potential risk of the used medical device that includes a nanomaterial, or is manufactured using

nanomaterials. The benefit weighing comes after the inventory on the risk. Even for highly beneficial medical devices not every risk can be acceptable.
In the text both the release of nanoparticles by, for example, degradation and wear is considered. In addition, in the last sentence also the generation of nano-sized particles by wear-and-tear in medical devices manufactured without the use of nanomaterials is clearly mentioned.

Page 50 to 52
Abbreviations and glossary section is adapted where needed.

Page 53 to 64.
References are updated according to the adapted texts.

Page 65-69.
The Annex is provided as extra information on the characterization methods for nanomaterials.