NOTE TO THE EUROPEAN COMMISSION

The preliminary report of the SCENIHR "Guidance on the Determination of Potential Health Effects of Nanomaterials Used in Medical Devices" is in public consultation.
The purpose of this review is to discuss the use of nanomaterials (NM) in medical devices (MD) and to provide information for the risk assessment of specific aspects that must be taken into account in assessing the safety of nanomaterials.

The usage of nanomaterials in medical devices can vary greatly. Examples are the use of nanomaterials as a medical device and administered to the patient as such (e.g. iron oxide nanomaterials or gold for heat therapy in treatments against cancer), nanomaterials in a paste formulation (e.g. composite dental filling), nanomaterials added to a medical device (e.g. silver nanoparticles as an antibacterial agent), fixed nanomaterials as a coating on implants to increase biocompatibility (e.g. nano-hydroxyapatite) or to prevent infection (e.g. nano-silver), or nanomaterials incorporated to enhance biomaterials (e.g. carbon nanotubes in a wall of the catheter). In all these cases, the risk of exposure to nanomaterials should be considered. It is further recognized that medical devices wear may lead to the generation of nanometer-sized particles, even when the medical device itself does not contain nanomaterials.

This note of the French authorities is to provide information to assist in the assessment of safety and risk assessment in the use of nanomaterials in medical devices that should be considered in conjunction with ISO 10993 -1: 2009. This guide emphasizes the need for special considerations with respect to the safety assessment of nanomaterials, because of their distinct properties, their interactions, and / or their effects, which may differ from conventional forms of these same materials.

Paragraph		Comments
On the overall document:		We suggest to change the name of the document to « Reflexion Paper » rather than to « Guidance » because it is not really a document of orientation (*guideline*), but rather a state of the art (*how things are at the moment)*. In general, this document illustrates the gap (of knowledge) in which the evaluation of the security of NM in MD currently is.
On the overall document:		The evaluation of a MD always has to comply with the health and safety requirements of the directives 93/42 and 90/385. The norms harmonised as ISO 14971 and the series ISO 10993 are tools that allow to comply to those requirements. We would like that the norm ISO 14971 is cited when the notion of risk is mentioned. Finally, the evaluation of risks of NM in MD should be coordinated with the provisions of the test methods described in the REACH framework, when revised.
On the overall document:		We would like that this document mentions the traceability of products containing NM. Is it possible to mention the possibility to declare on a European level the substances in MD by the producer in order to better apprehend (*judge*) the exposure.
3.3.1. **Physicochemical characterization of nanomaterials**	p. 14 l. 1. à 29 l. 32	We questioned the grounds on which the decision is based that the data related to a NM can be used for a NM with a different formulation or another NM. What are the parameters provided that show that there is a "similarity in physicochemical properties between NM"? The physicochemical properties of NM have been recognised to change in function of their size.
	p. 14 l. 29	We believe that the characterisation of impurities should be mentioned when presenting the physicochemical characterisation.

	p.15	***« table 1, column 1/ line 1 : « chemical composition/identity » »*** It is necessary for the document to discuss the topic of impurities in an entire new section. According to the report of Anses (2014), it is brought forward in the project ISO/TR 13014:2012 pertaining to the physicochemical characterisation of NM, the importance to not rely on the commercial characteristics provided by the suppliers and the need to characterise the impurities that can be the main cause of adverse effects. The suppliers, manufacturers need to qualify and quantify the impurities, in addition to their safety on human health. Moreover, the process of manufacturing of NM needs to be detailed. The impurities at nano scale can be generated by the manufacturing process. The (*end of the sentence is cut*)
3.3.2 Methods for characterization	P 17 ***Table 2***	« Table 2: Examples of methods for size 1 determination » Column 2 [Method] line 6 / AFM ; ***"scanned*** area ***is limited' :*** This word is not precise enough and we question whether this is related to the lateral resolution (approximately 10mm), vertical (order of Angstrom) or the viewable surface (100 nm^ au μπι2). Column 3 [Phase (liquid, solid, qas) and sensitivity]
		lines 5 ; 7 ; 8 : These boxes are empty and this raises questions on what this means.
		Colonne **4** [Particle distribution]
		line 4 / STM : This box is empty and this raises questions on what this means. line 6 / AFM : «Yes » should be indicated in this box, line 7 / SAXS ; « Yes » should be indicated in this box.
3.4 Uses of nanomaterials in medical devices	p.18 1.1	The different MD are categorised according to the norm ISO 109931:2009, Although the explanation of the classification is given in §3.5.4, this information should be added here to explain the choice of classification which is different from the directives 93/42 et 90/385.
	p.18 1.35 and 1.43 1.36 and 1.42	We question the coherence of these examples and suggest to organise them and group them by speciality type, to increase readability.

	p. 18 1.38 à 1.41	***« surface coating »*** Since « coatings » can be added on different types of MD, it would be useful to precise in the background.
	p.19 1.1 et 1.41	***"Specific types of medical devices"*** We questioned the relevance of adding a paragraph on the specific types of MD and suggest to integrate them in the paragraph related to the used classification.
	p.19 1.6	The citation of one particular manufacturer (Magforce) is surprising because there are other competing companies that provide this type of product. We question the relevance of this citation and we wonder whether this reference should not be taken out.
	p.19 1.13	***"Examples of applications under development"*** There is a distinction between the MD in clinical practice and the ones under development. For better readability, we suggest to reincorporate these examples of MD at the stage of development in the different classes of MD. Moreover, some examples of products under development have already reached the market.
	p.19	***"Silver nanocoatings for various catheters..." and "Catheters strengthened... "***
	1,18 et 1.20 p.19 1.21 p.19 1.4	We wonder why the distribution of these MD is done in two different classes.
		«Electrodes with laminin nanocoating... » We question the distribution of these MD in the classes « Invasive external communicating medical devices». ***Theranostics (therapy combined with diagnostics)*** On page 11 it is written that diagnostic MD will not be mentioned in this document. It is therefore surprising to see this example on page 19.
3.5. Exposure to nanomaterials from medical devices	p.20 35 1. à 33 1.	To refer to the report of AFSSAPS of 2011, it would be interesting to catch the attention of the reader to the fact that these norms do not respond to the specificity of NM and to explain why the norms are not adapted to these nanometric substances.
3.5.2. Exposure of patients to nanomaterials released from medical devices	p.22 1.1	We suggest to change this title 3.5.2 in ***"Exposure routes to nanomaterials released from medical devices exposure routes »*** in order to focus more on the route of exposure.

3,5.2.2 Invasive medical devices	p.22 1.33 à 1.44	***"The duration of contact with the patient is relatively short. "***
		We suggest to precise the definition of « short » because this adjective remains quite vague. Additionally, the example suggested for the dental exposure should precise that there is an exposure during the actions taken by the dentist in addition to an extended exposure due to (i) photopolymerisation which is incomplete in situ and (ii) exposure related to polishing.
3.5.4. Estimation of exposure for risk assessment	p. 23 1.15	We would like the norm ISO 14971 to be sited since management of risks in MD is mentioned.
	ρ 24 Table 3	***"Table 3: An estimation of potential externat and internai exposure as starting point for a risk evaluation for medical devices containing nanomaterials "***
		For a better understanding of the table, a justification and an explanation of the choice of wording « H=high, M=medium, L=low, N=negligible » is needed.
3.6.1. Introduction Toxicokinetics	p.25	In this paragraph, we would like the concept of physiologic barriers be discussed, being the barriers that control the organ primo-exposed to the blood or lymph (alvéolo-capillar, cutanious, intestinal) and the barriers that control the flow of blood to the systemic organs (hémato-encéphalic, placental, testicular).
	p. 25 1.15 à	***"For subgroups of certain solid nanomaterials, it is doubtful whether***
		We would like a scientific justification to be given for these statements, for some NM it is questionable whether metabolism is really taking place. De groups of NM with functional groups are susceptible to be metabolised. It is necessary to clarify this assertion in detail "these subgroups" and to justify why the metabolism does not need to be considered in this case.
3.6.2. Methods to evaluate toxicokinetics of na nomate rials Toxicokinetics	p. 26 1.10 à 1.11	***"Therefore, the use of such methodologies should be evaluated on a case by-case basis. "*** If the current methodologies are not adapted to NM, it is expected that this document would provide solutions or methods.
3.6.4 invasive medical devices	ρ 28 àI21	***"inhaled nanomaterials may migrate into the brain via the olfactory nerve"*** Although bibliographic reference have been cited, it would be advisable to cite one or two examples to prevent any confusion because this sentence could easily lead to the conclusion that all NM go through the hemato-encephatic barrier regardless of their chemical compositions and their size.

3.6.5. Conclusions on toxicokinetics of nanomaterials	p. 29 9-1. 01	***"In addition, consideration should be given to the potential for tissue accumulation and persistence of*** a ***mnomaterial (e.g. dissolution/degradation of the nanomaterial), for which repeated exposure and prolonged follow-up time may be necessary. "***
		We believe it is important to add that special attention should also be paid to the translocation of NM and target organs potentially rich in cells capable of phagocytosis such as the liver, spleen, bone marrow, (*sentence is cut)*
3.7.1 introduction	p. 29 1.34 à 1.36	***"Therefore, it is essentiel that tests are conducted using the same nanomaterial with the same chemical composition, size and size distribution, surface properties and purity/impurity profile as the substance present in the medical device"*** We would like to add that impurities also need to be characterised.
	p. 29 **I.** 43	***"However, in vitro tests may be useful for screening purposes, and to elucidate possible mode of action (Basketter et al, 2013)... "***
		The reference made to the publication of (Basketter et al., 2013) does not seem relevant because it does not deal with ***in vitro*** methods of NM.
	p. 29 I. 47	We would like to add that ***in vivo*** studies need to be carried out using the most realistic method of administration which means the one that is mostly related with the considered route of human exposure.
	p. 30 1.4	We would like that the global approaches « omiques » are also mentioned in this document.
3.7.2. Potential pitfalls in toxicity testina of nanomaterials	p. 30 1. 13 1 1	We would like to add that it is also necessary to use appropriate cellular models, appropriate to mimic human exposure which means cellular models that are capable of endocytosis, exocytosis, repair mechanism and apoptosis.
	p. 30 **1**.21	We would like to add that we have to ensure that the usage of high concentrations ***in vitro*** or excessive dosage ***in vivo*** can lead to a false interpretation of results. If possible, the studies ***in vivo*** need to be carried out using the most realistic method of administration, which means the one that is mostly related with the considered route of human exposure. Chronic exposures at low doses need to be privileged, taking into consideration that massive dosages of administration ***in vivo*** can lead to toxic effects non-specific to NM, difficult to extrapolate to a human exposure.

3.7.3 Toxicity testinq methods	p.32	In general, on the methods used ***(in vivo, in vitro),*** it seems important to remember and state before this chapter that: If possible, the studies ***in vivo*** need to be carried out using the most realistic method of administration, which means the one that is mostly related with the considered route of human exposure and it should be checked that the tested substance reaches the targeted organ. - You have to ensure in advance that NM are internalized by the cells used in the cell models. The test protocols will also have to be adapted to kinetic endocytosis and exocytosis in the selected cell models. - The cell lines used should be capable of supporting the reactive oxygen species (ROS). - Positive and negative controls should be validated and the methods used must be reproducible - The OECD methods must be adapted to NM. We would add that the toxicity to the nervous system is not mentioned and should be addressed, given the risk associated with this type of nanometric substances.
		We would add that the toxicity to the nervous system is not mentioned and should be addressed, given the risk associated with this type of nanometric substances. In general, the majority of the suggested tests are not validated.
3.7.3 Toxicity testinq methods Cytotoxicity	p. 32 I. 20	We would add that the NM themselves should not interfere with the systems in order to assess their toxicity. For NM with oxidizing properties, it is difficult to select cytotoxicity tests using the marker MTT, which is susceptible to oxidation (Lupu, 2013). Under these conditions, the risk of overestimation of cell survival is possible. ***Lupu AR, Popes cu T. (2013) The noncellular reduction of MII tetrazolium sait by Ti02 nanoparticles and its implications for cytotoxicity assays Toxicol In Vitro. 2013 Aug; 27(5):1445-50.***
	p. 32 **1.**23	We want to add a reservation *(a doubt)* on the usage of the 3T3 NRU test, as it was also shown that carbon-based NM could adsorb molecules of the neutral red dye and as a consequence give false positives (Monteiro -Riviere , 2009) (AFSSAPS 2011). ***Monteiro-Riviere, N. A.; Inman, A.* 0.; *Zhang, L. W. (2009) Limitations and relative utility of screening assays to assess engineered nanopariicle toxicity in* a *human cell line. Toxicology and Applied Pharmacology, 234 (2), 222-235.***

	p. 32 I. 21 à I. 24	We question the relevance of this comment in this paragraph. Rather, it is the presentation of an integrated strategy for oral toxicity which includes a cytotoxicity test. But no NM has been used to validate this model. If this test is quoted it would be useful to clarify that the ECVAM described this test: « EHRL ECVAM Recommendation on the 3T3 NRU Assay for Supporting the Identification of Substances Not Requiring Classification for Acute Oral Toxicity » ***https://eurl- ecvam. ire. ec. europa. eu/eurl-ecvam-recommendations/3i3- nru-recommendation***
3.7.3 Toxicity testinq methods Acute toxicity	p. 32 1.31-32	We question the appropriateness to do a test for acute toxicity. According to Anses (2014), chronic exposure to low doses should be favoured. The massive administrated doses in studies of toxicity can induce non-specific toxic effects of NM, difficult to extrapolate to human exposure. An overloaded dose can induce cytotoxicity and inflammation.
	p. 32 **1**.38	Moreover, no indication has been provided to us to prove whether these tests are relevant to NM.
3.7.3 Toxicity testinq methods Irritation activity	p. 32 I. 46	We wish to point out that it has been shown that the presence of NM (including carbon black and titanium dioxide) induced artefacts related to in vitro release of proinflammatory cytokines (Valle et al . 2009). This phenomenon, related to the adsorption of cytokines on nanoparticles, thus requires multiparametric evaluation. (AFSSAPS 2011). In addition, we ask what the suggested solutions are if these tests are not validated for NM. ***Val, S.; Hussain, S.; Boland, S.; Hamel, R; BaezaSquiban, A.; Marano, F. (2009) Carbon black and titanium dioxide nanoparticles induce pro-inflammatory responses in bronchial epithelial cells: need for multiparametric evaluation due to adsorption artifacts. Inhal Toxicol, 21 Suppl 1,115-22.***
3.7.3 Toxicity testing methods Delayed-type hypersensitivity	p. 33 I. 41-42	We wonder what the suggested solutions are if these tests to evaluate contact hypersensitivity are not validated for NM.

	p. 34 1.11	We would add that the absorption of NM or their recognition by human dendritic cells can also lead to phenomena of immunosuppression. Adjuvants effects caused by the NM may also be expected. (Afssaps 2011).
3.7.3 Toxicity testinq methods In vitro genotoxicity testing	p. 34 1.14 to 1.15	***"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. "*** It cannot be excluded that NM are genotoxic when its non-nano form has no genotoxic potential. Furthermore, the NM can cause inflammation, which causes oxidative stress (insertion into the mitochondria and the nucleus), resulting in an indirect or direct genotoxicity with NM in DNA and histones (SCENIHR 190109). We hope that this paragraph will be deleted or reformulated.
	p. 34 I. 36	Two ***in vitro*** tests have been suggested without any justification being given. It would have expected a justification of the recommended tests and the order in which they should be carried out. Moreover, we do not agree with the proposed tests.
		1. ***In vitro*** micronoyau (OECD 487) 2. ***In vitro*** cornet assay The cornet assay ***in vitro*** is not yet confirmed but is a much more robust test than the Ames test. However, studies are yet to be finalized related to the predictive capacity of the Cornet test in vitro and its reproducibility inter and intra -laboratory.
	p. 34 I. 38	We would add that the tests on mammalian cells (OECD 476) which use murine cells (L5178Y , CHO, V79) have some disabilities (*anomalies)* (detoxification enzymes , p53, etc.) and may overestimate the observed effects and cause a false evaluation.
	p. 34 I. 39-40	We want to add that we must first ensure that NM are internalized by the cellular models used here.

3.7.3 Toxicity testing method In vivo genotoxicity testing	p. 35 I. 8	We wish to clarify that some ***in vivo*** models may not be fully
	p. 35 1. 15-16	— ***"an in vivo micronucleus test (OECD 4 74)*** — ***an in vivo mammalian bone marrow chromosome*** We wish to remind you that these tests target hematopoietic cells. However, the bone marrow is not the tissue which is the most exposed to NM. Thus, the relevance of these tests on this tissue is questionable and should be carried out case by case, based on the identified target organs.
	ρ 35 1.17-1	— ***"an in vivo mammalian spermatogonial chromosome aberration test (OECD 483)"***
		— ***"a transgenic rodent gene mutation assay (OECD 488)"*** We question the relevance of the OECD test 483 if no accumulation of NM is shown in the testicles during distribution studies (pharmacokinetics) . We want to remind you about the OECD test 488, there are currently few laboratories which perfectly master this technique and therefore it cannot be used. Also, the generated data is currently limited.
	p. 35 1.41	We would like to add that the inflammation may be desired, for example by the dosage of mediators and/or pro-inflammatory markers, e.g. the inflammation ***in vivo*** can induce a secondary genotoxicity (eg Ti02 (Trouillcr et al, 2009)) and cause of carcinogenesis (Kundu et al ., 2008) .: - Trouillcr B, Reliene R, Westbrook A, Solaimani P, Titanium dioxide nanoparticles induce DNA damage and genetic instability ***in vivo*** in mice. ***Cancer Research*** 69(22),8784- - Kundu JK, Surh Y-J (2008) Inflammation; Gearing the journey to cancer. ***Mutation Research/Reviews in Mutation Research 659(1***

	p. 39 1.14	***"If additional tests are considered necessary, "*** This sentence is ambiguous and would need to be clarified. When positive or inconclusive results are obtained with the first-line test, for example, what should be the adopted strategy?
	p. 39 I. 19-20	***« No indication is available on the suitability of these tests designed for chemicals to assess the reproductive toxicity potential of nanoparticles. »*** This sentence should be put at the start of this chapter, at the recommendation of the tests. We may question the appropriateness of recommending tests that are not validated for NM.
	p. 39 1.38 à 1.43	We would like that this paragraph be reworded to clarify, first the effects on the development and secondly, the issue of animal
3.8 Evaluation of nanomaterials used in medical devices	p.40 1.6 1	Dans le tableau 4 : « ***Framework for specific nanomaterial toxicity testing based on potential release (exposure) oj nanomaterials from medical devices »*** could you add in a footnote page, for example, the meaning of "Phys : chem dat"?
	ρ 40 Table 4	We would like that an explanation is given to understand what criteria are used to differentiate low exposure, average exposure and high exposure? Column 1: ***"Testing Proposed"*** remains somewhat subjective. Temporal or quantitative criteria should be
3.8.5. Specific t'^es of medical devices	p.42 1.19 à 1.52	We question the appropriateness of a paragraph on the specific types of MD and propose to include them in the section related to
3.8.4. Invasive implantable medical devices à **3.8.6. Conclusions**	p. 42-43	For implantable MD containing NM, it is recommended to study the distributions and target organs, but no method is discussed in §3.8 .
4. Risk evaluation	p. 44 1.21-22 Figure 2	***« Figure 2: Risk assessment of nanomaterials used in invasive medical devises: a phase approach"*** The flowchart is not satisfactory as a whole for the following reasons : The level of impurities is not addressed. It is not known if this diagram takes into account whether the contaminants or impurities are to scale *(Cut sentence)*

		The release of the particles is discussed, but it is unclear if particles are generated due to sage or degradation of in situ or whether these particles correspond to impurities existing before implantation? Assessing the risk of MD with NM is based on the release of NM and the qualification of this release (negligible, low, significant, high ...). It should be noted that the release of NM is not addressed early on in the document. There is no mention of any analytical method, no threshold value determining negligible, low, significant or high passage. It is stated that the fate of leached particles must be considered, however, no tools are provided to be able to achieve this.
	p.44 1.4-5 Table 5	***"Table 5: Framework for risk assessment of nanomaterials used in medical devices"*** In addition, Table 5 offers, in function of the rate of leached particles and the destination of the MD, to make a complete, limited, very limited, or no evaluation. It is not specified in this document which tests need to be performed according to these four types of proposed assessments.
	p.44-46	In conclusion, this section 4 "Risk assessment" provides a methodology of assessment that cannot be put in practice in view of the uncertainties in the exposure data, and thus the release, and in light of the non-applicability of currently assessment methods available for NM. It also places the responsibility on the appraiser advocating for a case-by-case basis. This document seems to be primarily an inventory which is needed. This document provides a guidance that will give a testing strategy, supported by examples of evaluation process.

Références to be checked on other document.