WORKING GROUP ON NEW AND EMERGING TECHNOLOGIES IN MEDICAL DEVICES (N&ET WORKING GROUP)

JULY 2007

REPORT ON NANOTECHNOLOGY TO THE MEDICAL DEVICES EXPERT GROUP

FINDINGS AND RECOMMENDATIONS

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1. Scope of this document

This document covers medical devices manufactured utilising nanotechnology.

2. Aim of this document

The aim of this document is to consider the adequacy of the existing medical devices regulatory regime in relation to the use of nanotechnology in medical devices, identify any shortcomings and, where deficiencies are identified, make recommendations to the Medical Devices Expert Group on the best ways of addressing them.

3.Definition of nanotechnology

Nanotechnology is the design, characterisation, production and application of structures, devices and systems by controlling shape and size at the nanometre scale [1].

4. History of the N&ET Working Group

During the Competent Authority for Medical Devices meeting in Rotterdam in July 2004, competent authorities discussed the regulatory challenges raised by new and emerging technologies such as robotic surgery, nanotechnology and minimally invasive surgery. Participants examined the following questions:

- what are the major risks of these new technologies ?
- if we compare these with the essential requirements of the current medical device legislation, are they properly covered or would it be necessary to adapt legislation?

The overall conclusion was that this topic needed further discussion.

At the MDEG meeting in October 2004 the Commission proposed that a Working Group on New & Emerging Technologies be formed and the Dutch delegation was provisionally asked to chair it.
As a first step, EUCOMED, one of the European trade federations, and the Dutch delegation jointly organised a Workshop on New & Emerging Technologies in July 2005. At this Workshop, open to all stakeholders, a broad overview of the new areas of medical technology was given.
At the MDEG meeting of July 2005, the mandate for the Working Group on N&ET was confirmed. The first meeting was held on 15 November 2005 and the Working Group elected the Dutch delegation as its chair.
Subsequently, the Working Group met on 29 March 2006, 23 October 2006 and 13 April 2007.
The Group agreed on the terms of reference and the work programme and nanotechnologies was identified as the first work item.

5. Working method

At the first meeting the Working Group agreed to deal with new and emerging technologies according to the following five-stage approach:

a. Identification
b. Definition
c. State of the art
d. Assessment of existing regulations
e. Recommendations for dealing with any deficiencies of regulations.

For nanotechnology, this five-stage approach was applied as follows:

a. Identification

The Working Group identified nanotechnologies as the first work item.

b. Definition

It was decided that the definition of nanotechnology given in the 2004 report of the UK Royal Society & Royal Academy of Engineering [1] would be used. This definition was also adopted in the SCENIHR opinion [2] and the reports from the Dutch RIVM [3,4].

c. State of the art

This item was prepared by a small group of volunteers, who selected relevant examples of nanotechnology products covering the broad range of possible applications. The basis for this selection was the RIVM report on the state of the art of nanotechnology in medical applications [3] and contributions from group members.

Important criteria for the inclusion of examples included the coverage of different particle sizes, production of nanostructures bottom-up or top-down, MDD/IVDD/AIMDD products and borderline products.

On 29 March 2006 the Working Group analysed these examples and drafted two shortlists of generic regulatory risk assessment issues: one for MDs/AIMDs and one for IVDs. These regulatory risks have been further analysed and the conclusions are included in this document.

d. Assessment of existing regulations

Two members/authors, assisted by two groups of members/commentators, drafted two separate documents, answering the question whether the MDD/AIMDD or the IVDD would cover the generic risk assessment issues.

e. Recommendations for deficiencies

The documents under d. also contained proposals on how these generic risk assessment issues should be covered. Subsequent drafts of these two documents were discussed at the N&ET meetings of 23 October 2006 and 13 April 2007. This Report to the MDEG reflects the outcome of these discussions.

6. Concluding Position of the N&ET Working Group

In general, the N&ET Working Group considers the medical device legislation suitable to deal with medical devices manufactured utilising nanotechnology. The medical device legislation is based on risk management, and this risk management approach is in principle suitable to address all kinds of risks, including the risks associated with medical devices manufactured utilising nanotechnology.

The specific risks for nanotechnology applications appear to be related to the use of nanoparticles, more specifically to free nanoparticles. Nanoparticles may behave differently from the bulk of the same material/compound and this may result in altered biological (toxicological) behaviour.
Note: It is acknowledged that solid materials with surface nanoscale features associated with coatings, or with other nanotopographical features, may also have specific and unique physicochemical properties (SCENIHR opinion)[5].

The group also considered that, as we are dealing with risks that are partly new and not fully known to all stakeholders, it would be appropriate to develop regulatory guidance, e.g. a MEDDEV document for products covered by the AIMDD, MDD or IVDD which:

1/ explains the nature of the risks that should be taken into consideration ;

2/ provides possible solutions to manage these risks ;

3/ outlines the organisational structure of the voluntary sharing of experience gained for such products by the manufacturers during a period of 3 -5 years, to allow better understanding of the application of nanotechnology ;

4/ provides an appropriate mechanism for collecting the information in a Voluntary Reporting Scheme;

5/ provides guidance on the necessary actions during the post -marketing phase;

6/ helps in identifying the appropriate regulatory pathways towards the future as our knowledge progresses;

7/ explains which parts of this regulatory guidance document are applicable to IVDs .

The group also considered that the current medical device vigilance system does not need to be adapted: it is sufficiently generic in its approach to deal with nanotechnology issues in an adequate way. However, it was stressed that there is a need for an active system of post-market surveillance by the manufacturers, as required by the Directives.

7. Summary of findings

A. The MDD and AIMDD

1. Introduction of a specific classification rule could be considered in order to make sure that any potentially high-risk nanotechnology applications will be classified in Class III. Such devices require a careful case-by-case risk assessment and it is desirable that independent verification of the risk assessment should always take place. The most appropriate way to guarantee this was felt to be the classification of these devices in Class III. This should, however, not create an unnecessary burden, so it should be formulated very carefully. Taking into account the generic risk assessment issues, a proposal could be: "All devices incorporating or consisting of particles, components or devices at the nanoscale are in Class III unless they are encapsulated or bound in such a manner that they cannot be released to the patient 's organs, tissues, cells or molecules".

   Note 1: There is no scientifically based cut-off point to define nanoscale. The size below which materials can display specific properties varies for different materials. Several relevant groups such as the OECD[6] and SCENIHR[5] have used a working definition for nanoscale: the size typically ranging between 1 and 100 nm, for at le ast one dimension of the nanomaterial. Although this definition was not developed for regulatory purposes, it does seem an appropriate way forward.

   Note 2: After careful consideration, it was decided to confine the proposed classification rule to free nan oparticles, even though it is acknowledged that solid materials with surface nanoscale features associated with coatings, or with other nanotopographical features, may also have specific and unique physicochemical properties (SCENIHR opinion)[5].

   Note 3: It is recommended that the functioning of the classification rule be reviewed after a three- or five-year period.

2. Products with a coating of nanoparticles present a risk of accidentally releasing nanoparticles during use; such situations do not seem to diffe r significantly from traditional implants (e.g. hip prostheses) which can also generate wear particles, including nanoparticles. The risk assessment should address this issue.

3. Risk management is an integral part of the way manufacturers comply with medical device legislation. By obliging manufacturers to take account of "the generally acknowledged state of the art", the Medical Device Directives ensure that, before a medical device can be CE-marked and placed on the market, the manufacturer must take into account not only risks of established technology, but also those associated with any new and emerging technologies, such as nanotechnology.

In this context of risk assessment, it is particularly interesting to note that in its Opinion on "The appropriatenes s of existing methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnologies", the Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR)[2] concluded (on page 55) that:
"In the absence of data to the contrary, it cannot be assumed, for risk assessment purposes, that the nanoparticle form of a chemical(s) has similar effects on biological systems to those of the same chemical in other physical forms. To maintain a high level of public health, occupational health and environmental protection in the European Union, it is essential that a specific risk assessment is conducted along the lines proposed above if there is any potential for humans and the environment to be exposed to particular forms of nanoparticles. The use of nanoparticles requires a special focus in the risk assessment taking into account the size and application of the nanoparticles, as one single chemical can have a different toxicological risk depending on its size and physical features. "

4. For MDD/AIMDD medical devices incorporating nanotechnology , the risk assessment and management should pay special attention to specific physico - chemical characteristics and toxicological and toxicokinetic properties associat ed with free nanoparticles in relation to their application area.

5. Adaptation of the essential requirements is not necessary for devices incorporating or consisting of free nanoparticles .
   Apart from the general essential requirements in Annex I, Sections 1 and 2, the following essential requirements are considered to be relevant to and to sufficiently cover devices manufactured utili sing nanotechnology:
   - Section 7.1: "particular attention must be paid to: the choice of materials used, particularly as rega rds toxicity (…), compatibility between the materials used and biological tissues, cells and body fluids (...)";
   - Section 7.2: "the devices must be designed, manufactured and packed in such a way as to minimise the risk posed by contaminants and residues (…)";
   - Section 7.5: "the devices must be designed, manufactured and packed in such a way as to reduce to a minimum the risks posed by substances leaked from the device (…)";
   - Section 9.2: "the devices must be designed, manufactured and packed in such a way as to remove and minimi se as far as possible: the risk of injury, in connection with physical features (…), risk connected with reasonable foreseeable environmental conditions (…)".

6. It was stressed that there is a need for an active post -market surveillance system, as required by the Directives ("undertaking by the manufacturer to institute and keep up to date a systematic procedure to review experience gained from devices in the post - production phase, including the provisions referred to in Annex X, an d to implement appropriate means to apply any necessary corrective action").

7. Since current knowledge is very limited, it is recommended that a Voluntary Reporting Scheme be considered in order to share experience with the risk assessment of nanotechnology with relevant stakeholders.

8. Given the potentially different biological/toxicological behaviour of nanoparticles, new mandates for standardisation, e.g. a review of the EN ISO 10993 series for the Biological Evaluation of Medical Devices and/or a new part in this series indicating specifics of nanotechnology products for the purposes of biological evaluation, seem warranted. Perhaps a structured checklist of the possible mechanisms to look for might be helpful for a comprehensive discussion of the risks in the risk management process.

   Note: It was noted that the Commission had issued a general mandate on nanotechnology and nanomaterials, asking CEN to provide a list of standards to be developed/revised[7].

9. In contrast to the IVD Directive, the MD and AIMD Directives do not have specific requirements on the safe disposal of devices into the environment.

   It was felt that the issue of waste disposal of devices manufactured utilising nanotechnology could be covered adequately by general Community rules on waste disposal. However, the issue of disposal of products containing nanoparticles in general (and not specific medical devices) has not yet been explored by the relevant Committees.

B. The IVDD

1. Since IVD tests are carried out on samples taken from the human body and are analysed in vitro, the potential risks, if any, arising from the use of nanotechnology in the manufacture of IVD medical devices are limited to those that may occur to the user in the course of using the device and during storage, transport and waste disposal of the device. For the majority of IVD medical devices, patients are not themselves at any potential risk since they do not come into any contact with the device. The only exceptions to this are:

   a/ devices for IVD purposes with an invasive body contact (MEDDEV 2.14/1 rev 1 paragraph 6), or

   b/ IVD medical devices for self testing.

   The specific risk inherent in the use of nanotechnology for these exceptions appears to be related to the use of free nanoparticles.

   Note: It is acknowledged that solid materials with surface nanoscale features associated with coatings, or with other nanotopographical features, may also have specific and unique physicochemical properties (SCENIHR opinion)[5].

2. There is currently no need to address the exceptions described in point 1 above by amending Annex II to the IVD Directive or by creating an additional Annex.

   Since current knowledge is very limited, it is recommended that a Voluntary Reporting Scheme be set up in order to share experience with the risk assessment of nanotechnology with relevant stakeholders. The experience gained in this scheme will allow for a review in 3-5 years.

3. Modification of the essential requirements (ERs) is not necessary since the existing ERs include requirements ensuring the safety of the user, storage, transport and safe waste disposal irrespective of the materials and technology used - see Annex I, Sections A1, B1.2 and B 3.5.

4. Risk management is an integral part of the way manufacturers comply with medical device legislation. By obliging manufacturers to take account of "the generally acknowledged state of the art", the Medical Device Directives ensure that, before a medical device can be CE-marked and placed on the market, the manufacturer must take into account not only risks of established technology, but also those associated with any new and emerging technologies, such as nanotechnology. In this context of risk assessment, it is particularly interesting to note that in its Opinion on "The appropriateness of existing methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnologies", the Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR)[2] concluded (on page 55) that:
   "In the absence of data to the contrary, it cannot be assumed, for risk assessment purposes, that the nanoparticle form of a chemical(s) has similar effects on biological systems to those of the same chemical in other physical forms. To maintain a high level of public health, occupational health and environmental protection in the European Union, it is essential that a specific risk assessment is conducted along the lines proposed above if there is any potential for humans and the environment to be exposed to particular forms of nanoparticles. The use of nanoparticles requires a special focus in the risk assessment taking into account the size and application of the nanoparticles, as one single chemical can have a different toxicological risk depending on its size and physical features."

5. The current provisions in the IVD Directive regarding conformity assessment, based as they are on the parameters to be detected, can be considered adequate and appropriate with regard to the use of nanotechnology in the manufacture of IVD medical devices. However, in carrying out their conformity assessment, manufacturers may seek to comply with available harmonised (since this would provide a presumption of conformity with the ERs) and/or international standards.

6. It was stressed that there is a need for an active post-market surveillance system, as required by the Directive ("undertaking by the manufacturer to institute and keep up to date a systematic procedure to review experience gained from devices in the post-production phase, including the provisions referred to in Annex III(5), and to implement appropriate means to apply any necessary corrective action").

8. Recommendations

A. The MDD and AIMDD

1. Request the Commission to introduce by a suitable legal procedure the following classification rule in Annex IX to the MDD: "All devices incorporating or consisting of particles, components or devices at the nanoscale are in Class III unless they are encapsulated or bound in such a manner that they cannot be released to the patient's organs, tissues, cells or molecules".
   The functioning of this classification rule should be reviewed after a three- or five-year period.

2. Consider new mandates for standardisation, e.g. a review of the EN ISO 10993 series for the Biological Evaluation of Medical Devices and/or a new part in this series indicating specifics of nanotechnology products for the purposes of biological evaluation. A structured checklist of the possible mechanisms to look for might be helpful for a comprehensive discussion of the risks in the risk management process.

   Note: It was noted that the Commission had issued a general mandate on nanotechnology and nanomaterials, asking CEN to provide a list of standards to be developed/revised[7].

3. Consider a Voluntary Reporting Scheme in order to share experience with the risk assessment of nanotechnology with relevant stakeholders.

4. Develop regulatory guidance, e.g. a MEDDEV document, which explains the nature of the risks that should be taken into consideration, provides possible solutions to manage these risks, and helps in identifying the appropriate regulatory pathways. Furthermore, this document can provide guidance on the necessary actions during the post-marketing phase. The MEDDEV should also provide an appropriate mechanism for the proposed Voluntary Reporting Scheme.

5. Include guidance with regard to the conduct of clinical investigations with nanotechnology products, e.g. special exclusion criteria, in the proposed regulatory guidance document referred to in recommendation 4 above.

B. The IVDD

1. Consider a Voluntary Reporting Scheme in order to share experience with the risk assessment of nanotechnology with relevant stakeholders.

2. Develop a document covering the potential risk for the patient and/or user becoming exposed to free nanoparticles, e.g. a MEDDEV document, providing guidance for the use of nanotechnology in IVD medical devices. Relevant issues for IVDs should be included in the regulatory guidance document advocated in recommendation 4 for the AIMDD/MDD set out above.

   Note: The potential exposure of workers during the manufacture of IVD medical devices is not within the scope of the IVD Directive but is covered by other Directives and regulations concerning worker safety.

3. Recommend that CEN/TC 140 and ISO/TC 212 liaise with ISO TC229/CEN/TC 352 to verify the need to revise/develop standards for IVD medical devices containing nanotechnologies.
   Note: It was noted that the Commission had issued a general mandate on nanotechnology and nanomaterials, asking the CEN to provide a list of standards to be developed/revised[7].

9. References

[1] The Royal Society & The Royal Academy of Engineering (2004). *Nanoscience and Nanotechnologies: Opportunities and Uncertainties.* The Royal Society, London, UK.

[2] Modified opinion (after public consultation) on "The appropriateness of existing methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnologies". Adopted by the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) during the 10th plenary meeting on 10 March 2006. Prof. D. Williams (chair and rapporteur), Dr M. Amman, Dr H. Autrup, Prof. J. Bridges, Dr F. Cassee, Prof. K. Donaldson, Prof. E. Fattal, Prof. C. Janssen, Dr W. de Jong, Dr T. Jung, Prof. J. Marty, Prof. K. Rydzynski. http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_003b.pdf

[3] B. Roszek, W.H. de Jong, R.E. Geertsma (2005). Nanotechnology for medical applications: state-of-the-art in materials and devices. RIVM-report 265001001. RIVM, National Institute for Public Health and the Environment, Bilthoven, the Netherlands. http://www.rivm.nl/bibliotheek/rapporten/265001001.html.

[4] W.H. de Jong, B. Roszek, R.E. Geertsma (2005). Nanotechnology in medical applications: Possible risks for human health. RIVM report 265001001. RIVM, National Institute for Public Health and the Environment, Bilthoven, the Netherlands. http://www.rivm.nl/bibliotheek/rapporten/265001002.html.

[5] Opinion on the appropriateness of the risk assessment methodology in accordance with the technical guidance documents for new and existing substances for assessing the risks of nanomaterials. Adopted by the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) during the 17th plenary meeting on 29 March 2007. Prof. D. Williams (chair and rapporteur), Prof. J. Bridges, Dr W. De Jong, Dr T. Jung, Prof. K. Rydzynski, Prof. P. Borm, Prof. K. Donaldson, Prof. W. Dekant, Dr T. Fernandes, Prof. H. Greim, Prof. C. Janssen, Prof. J. Jokiniemi, Prof. W. Kreyling, Dr K. Savolainen
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[6] OECD – Working Party on Manufactured Nanoparticles. Draft working definition on manufactured nanomaterials. ENV/CHEM/NANO(2007)4. 4 April 2007.

[7] Document CEN/TC 352 N55: Mandate addressed to CEN, CENELEC and ETSI for the elaboration of a programme of standards to take into account the specific properties of nanotechnology and nanomaterials