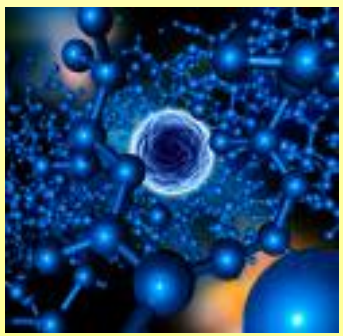
11th Conference of the Global Harmonization Task Force

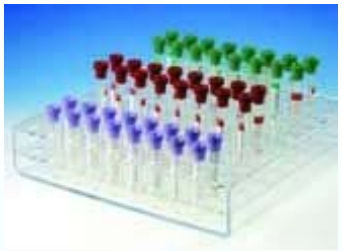
October 3-4, 2007 Washington, D.C

IVD devices incorporating Nanotechnologies: European Commission Report on Nanotechnologies in Medical Devices – Nanotechnologies and the IVD Directive



Benny Ons
BD Europe

Nanotechnologies?



Miniaturization

Change of scale

What is meant by Nanotechnology in the context of IVD Medical Devices?

Nanotechnology is concerned with the use of elements at the nanoscale level.

Nanotechnologies is used because it offers distinct practical advantages including being;

- more sensitive,
- more focused,
- used earlier,
- quicker,
- using less sample and
- additional parameters.

Examples of nanotech in the IVD industry

- The GeneChip (trademark) Affymetrix
- Microarray Genome screening
- Biosensors Optolab card
- Microfluidics

Is the IVD Directive suitable for IVD medical devices based on nanotechnology and/or involving nanomaterials

Definition of an IVD Medical Device

"... any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment or system, whether used alone or in combination, intended by the manufacturer to be used **in vitro for the examination of specimens, including blood and tissue donations, derived from the human body**, solely or principally for the purpose of providing information:

- concerning a physiological or pathological state, or
- concerning a congenital abnormality, or
- to determine the safety and compatibility with potential recipients, or
- to monitor therapeutic measures."

⇨ The majority of IVD medical devices will not have any toxicological or other harmful effect on the patient

However the following aspects have to be considered:

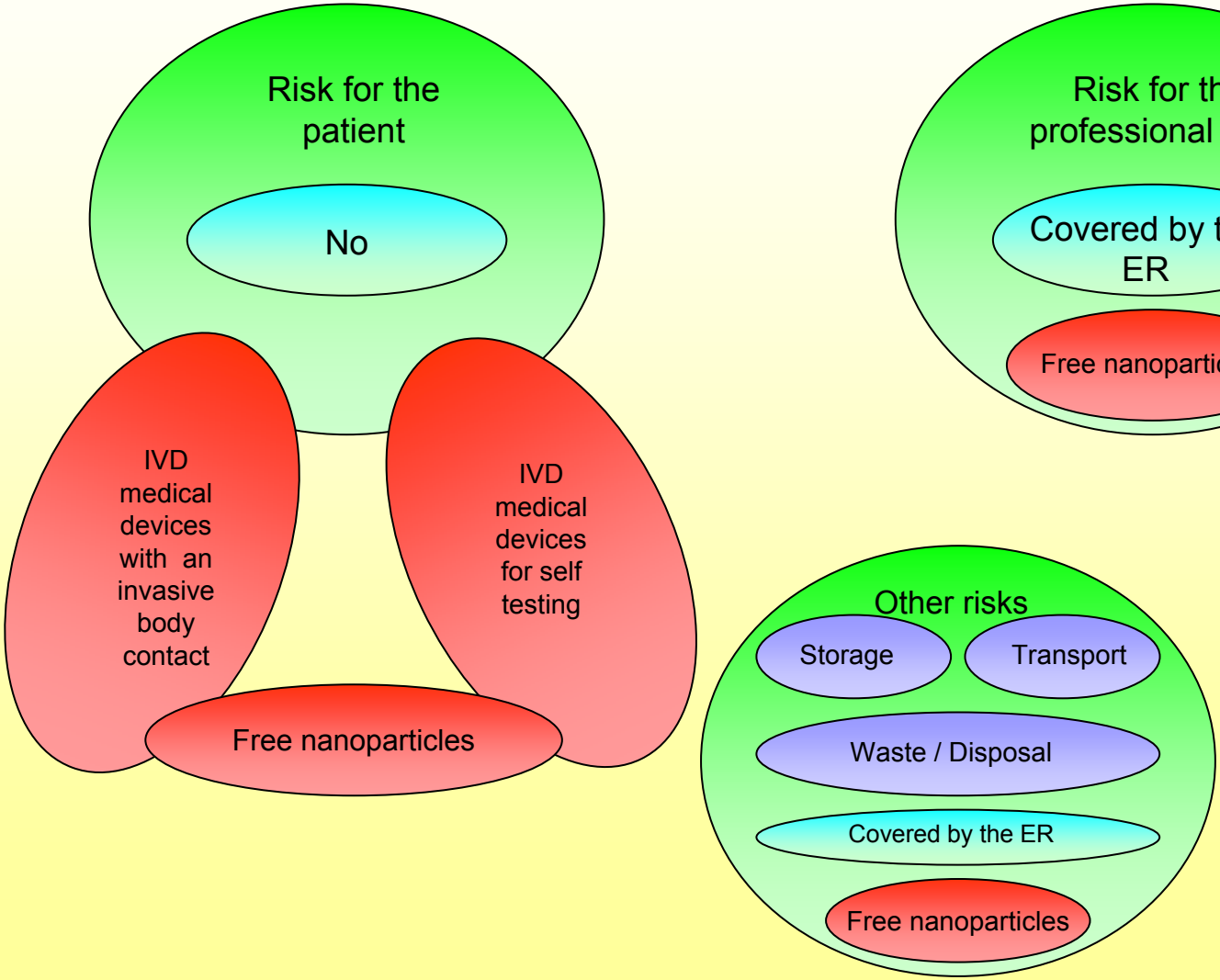
Aspects to consider when nanomaterials are used

1) Though the majority of IVD medical devices will have no toxicological or other harmful effect on a patient since the IVD testing is done in vitro on human samples external to the patient, some IVD medical devices do have an invasive body contact (MEDDEV 2.14/1 rev 1 paragraph 6, e.g. Strips with an integrated measuring function).

2) Regarding the use of chemicals, the new REACH legislation concerns only the chemical structure of compounds. It does not require a risk analysis related to their size and physical aspects.

3) The difference between IVD intended for professional use and those for self-testing (lay person as user): whereas professional use is more likely to involve a controlled environment of use, a controlled waste disposal, and well-trained users who are aware of the potential risks of the product, such knowledge and control are likely to be missing when lay users are concerned.

Risk of IVD medical devices incorporating nanotechnologies



Essential requirements

Annex I Section A 1

"The devices must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will not compromise, directly or indirectly, the clinical condition or the safety of the patients, the safety or health of users or, where applicable other persons, or the safety of property. Any risks which may be associated with their use must be acceptable when weighed against the benefits to the patient and compatible with a high level of protection and safety."

Annex I Section A 2

"The solutions adopted by the manufacturer for the design and construction of the devices must conform to safety principles, taking account of the generally acknowledged state of the art.

In selecting the most appropriate solutions, the manufacturer must supply the following principles in the following order:

- *eliminate or reduce risks as far as possible (inherently safe design and construction)*
- *where appropriate take adequate protection measures in relation to risks that cannot be eliminated,*
- *inform users of the residual risks due to any shortcomings of the protection measures adopted."*

Annex I Section A 5

"The devices must be designed, manufactured and packed in such a way that their characteristics and performances during their intended use will not be adversely affected under ***storage and transport conditions*** *(temperature, humidity, etc.) taking account of the instructions and information provided by the manufacturer."*

Annex I Section B 1.2

Annex I Section B 1.2 is particularly relevant to the chemical and physical properties of an IVD whether in the form of nanoparticles or not.

"The devices must be designed, manufactured and packed in such a way as to reduce as far as possible the risk posed by ***product leakage, contaminants and residues to persons*** *involved in the* ***transport, storage and use*** *of the devices taking account of the intended purpose of the products."*

Annex I Section B 3.2

"Devices must be designed and manufactured in such a way as to reduce as far as possible the risks linked to their use in conjunction with materials, substances and gases with which they may come into contact during normal conditions of use."

Annex I Section B 3.3

"Devices must be designed and manufactured in such a way as ***to remove or reduce as far as possible the risk of injury related to their physical features*** *(in particular aspects of volume x pressure, dimension and, where appropriate, ergonomic features)."*

Annex I Section B 3.5

"*Devices must be designed and manufactured in such a way as to facilitate the management of* ***safe waste disposal****."*

Information to be supplied by the manufacturer

Following the analysis of the ER the identified and remaining risks have to be mentioned in the information supplied by the manufacturer as set out in Annex I Sections 8.4 (labels) and 8.7 (Instructions for Use(IFU)).

Annex I Section B 8.4(h) - Labels

*"Any particular **storage and/or handling conditions**."*

Annex I Section B 8.4(j) - Labels

*"**Appropriate warnings and/or precautions to take**."*

Annex I Section B 8.7(a) - IFU

This section refers to all sections of the labels also including the points Annex I 8.4(h) and Annex I 8.4(j) as identified above.

Annex I Section B 8.7(n) - IFU

"all the information needed to verify whether the device is properly installed and can operate correctly and safely, plus details of the nature and frequency of the maintenance and calibration needed to ensure that the device operates properly and safely, information about safe waste disposal."

Annex I Section B 8.7(p) - IFU

"The necessary instructions in the event of damage to the protective packaging and details of appropriate methods of resterilisation or decontamination."

Annex I Section B 8.7(s) - IFU

"Precautions to be taken against any special, unusual risks related to the use or disposal of the device including special protective measures, where the device includes substances of human or animal origin, attention must be drawn to their potential infectious nature."

Risk Analysis

Risk Analysis

Annex I Section A 1 places an overall and extensive requirement on IVD manufacturers as regards risks generally – irrespective of the technology involved. In other words, the IVD Directive is technology independent.

Specific aspects of risk assessment for IVD medical devices

For IVD medical devices incorporating nanotechnology the risk assessment required by the IVD Directive should focus on the following specific elements associated with free nanoparticles:

- the chemical characteristics of the components
- the physical characteristics of the components
- the application area (exposure of the user/patient)

In the risk analysis particular attention should also be given to the features of the individual nanoparticles used, as a decomposition or dissociation of the applied nanoparticles cannot be ruled out.

In general the risk analysis should take into account whether the nanomaterials are biodegradable or not (accumulation, long-term persistence) and consider the effectiveness of destruction methods.

Conformity assessment of IVD medical devices incorporating nanotechnology

Over the years a variety of different technologies has been used for IVD medical devices and miniaturisation/automation have been introduced into the measuring methods.

Irrespective of the technology or technologies involved, risk assessment and risk management are at the very root of the IVD Directive and the results of the manufacturer's risk analysis and management are required to form part of the technical documentation that has to be kept available.

The IVDD places on the manufacturer an obligation to take account of "the generally acknowledged state of the art"

This obliges a manufacturer to not only take into account the risks of established technologies but also those associated with any new and emerging technologies such as nanotechnology.

⇒ the use of a new technology, such as nanotechnology, in the manufacture of an IVD medical device is anticipated and covered by the IVD Directive

→ no need to change the conformity assessment requirements.

Conclusion - Findings

1) For IVD medical devices potential risks that arise from nanotechnology are limited to those that may occur:
   - to the user in the course of using the device
   - during storage, transport and waste disposal

   ⇨Majority of IVD medical devices – no risk for the patient except for:

   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.

   In these exceptions the risk would only come from free nanoparticles

2) No need to amend Annex II (refer to the recommendations)

3) No modification of ER needed as they include sufficient elements to cover risks associated with nanotechnology.

Conclusion - Findings

4) As risk management is an integral part of the manufacturer's assessment before placing a device on the market, the manufacturer must take into account not only risks of established technology but also risks associated with new and emerging technologies such as nanotechnology.

5) Current provisions in the IVD Directive regarding conformity assessment can be considered adequate and appropriate as they are based on the parameter to detect.

6) As required by Annex III (5) of the IVD Directive a manufacturer is obliged to set up and keep up to date a systematic procedure to review experience gained from devices in the post production phase.

Conclusion - Recommendations

1) To consider a Voluntary Reporting Scheme in order to share the experiences with the risk assessment of nanotechnology with relevant stakeholders.

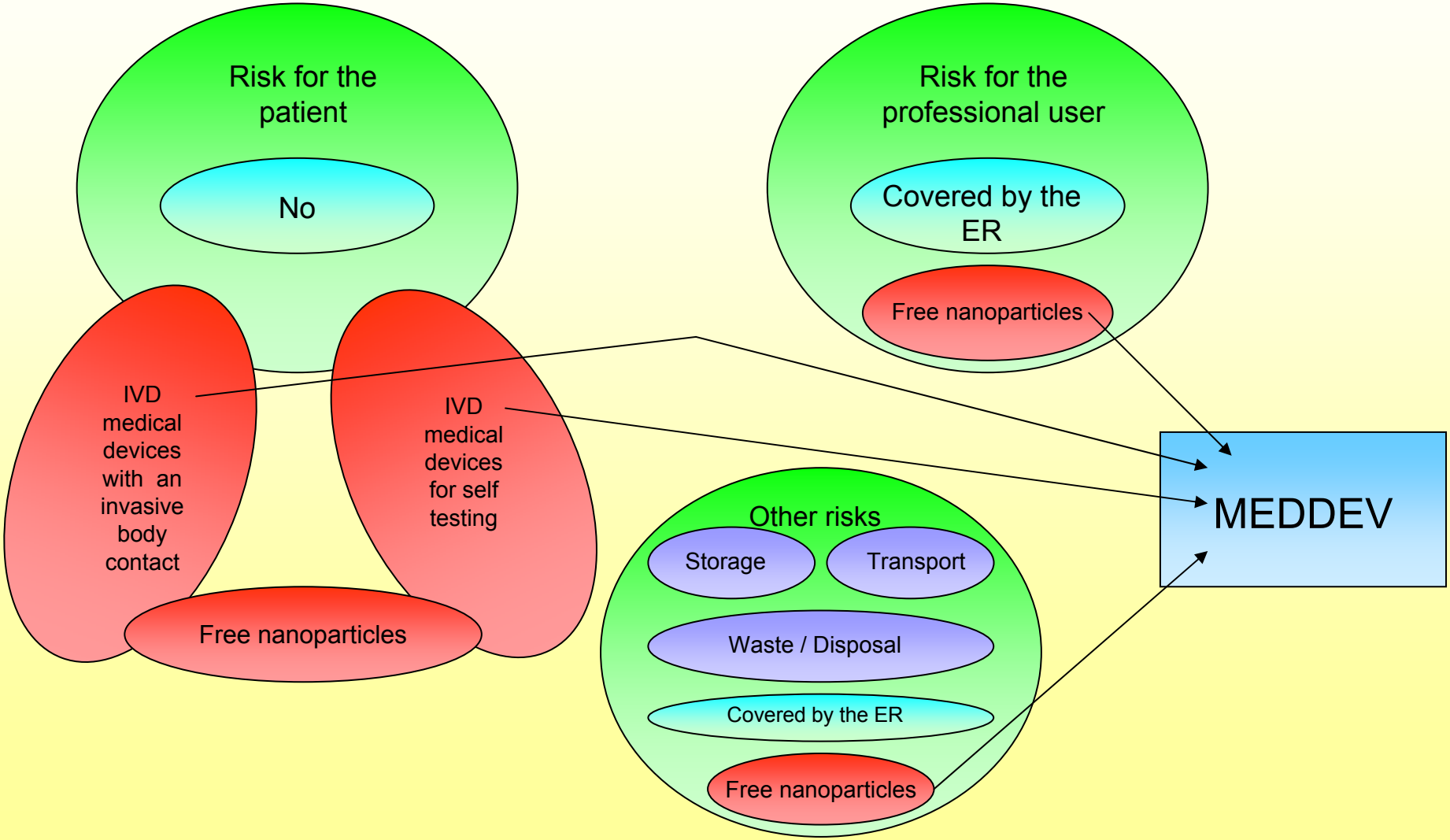
2) To cover the potential risk for the patient and/or user becoming exposed to free nanoparticles in a document, e.g. a MEDDEV, and to provide guidance for the use of nanotechnology in IVD medical devices, it is recommended to include relevant issues for IVD medical devices in the regulatory guidance document under recommendation 4 for AIMDD/MDD above.

   Note: The potential exposure of workers during the manufacturing 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) To recommend CEN/TC 140 and ISO/TC 212 to 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 issued a general mandate asking CEN to provide a list of standards to be developed/revised.

Risk of IVD medical devices incorporating nanotechnologies



Thank You!

Questions ?

Benny Ons
Director, Regulatory Affairs & Quality Management
BD Europe
Tel: +32-53-72.04.02
E-mail : benny_ons@europe.bd.com
October 2007