Eric Mayes, CEO

March 7th, 2018

Nanotechnology Industries Association

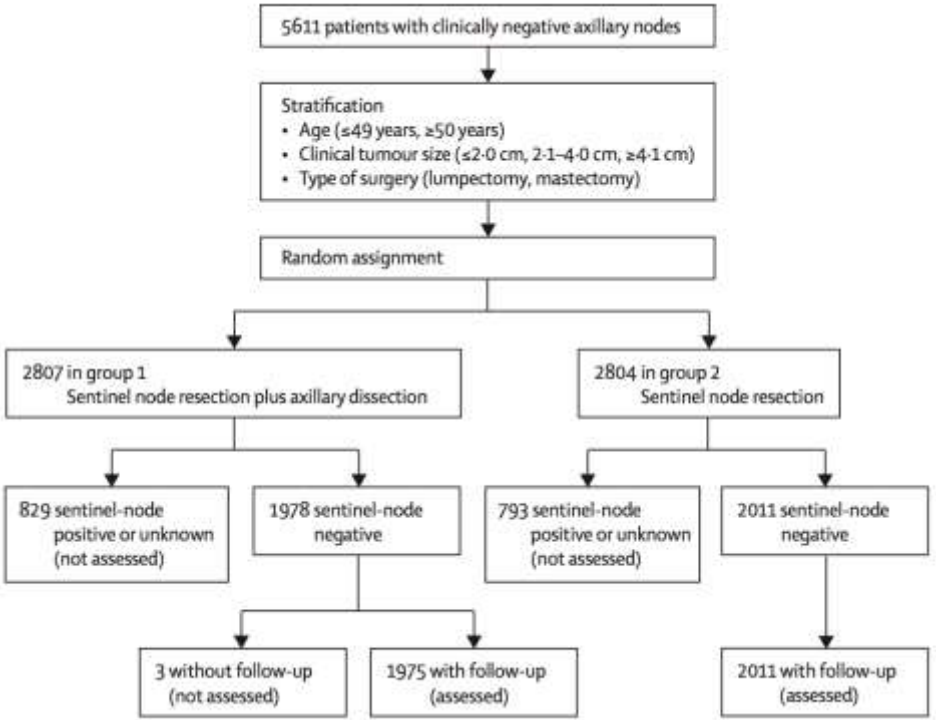
Nanomedicine: Diagnostics and therapeutics advancing through nanotechnology

The Clinical Need

- The global incidence of breast cancer is 1.7m annually and is the leading cause of cancer death in women
- Breast cancer incidence is projected to reach 3.2m by 2030 due to continued demographic changes*
- When cancer is confirmed, it's 'stage' must be established to decide next-steps for treatment – $T_{1-4}N_{0-3}M_{0-1}$ system (Tumour, Nodes, Metastasis)
- Sentinel lymph node biopsy (SLNB) is the best method for staging nodes
- However, only 1 in 6 patients globally receives the gold-standard of care

*Ginsburg, O. et al. The global burden of women's cancers. The Lancet (2016). doi:10.1016/S0140-6736(16)31392-7

NSABP B-32 Trial (May 1999 to Feb 2004)



- A sentinel lymph node biopsy (SLNB) is where only 1-2 lymph nodes are removed and analysed
- The Lancet, October 2010: Results from 5,611 women across 80 North American institutions
- Confirmed equivalent survivability at 5 years between patients with SLNB and those with axillary lymph node dissection (ALND) – established SLNB as the gold-standard of care

The Surgical Need

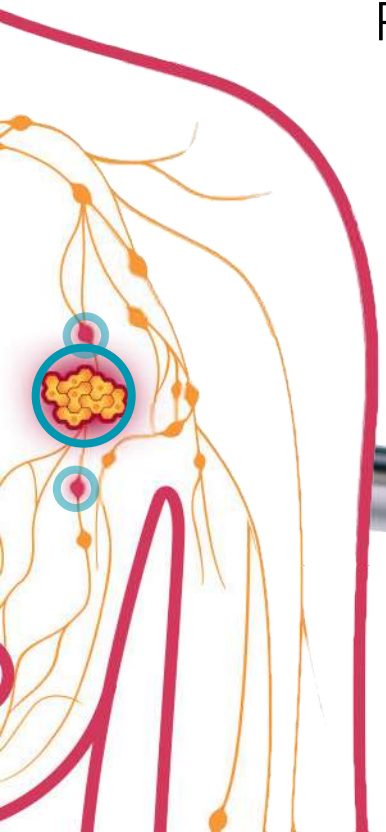
Primary Tumour

Remove the tumour and a sufficient margin

Sentinel Lymph Nodes

Remove the lymph node(s) first in line to drain from the tumour

Standard of Care



Primary Tumour

Hook wire localisation

- 25% of patients require follow-up surgery to remove residual cancer
- Surgery scheduled on same day as wire placement
- Wire limits surgical approach to tumour, impacting cosmesis

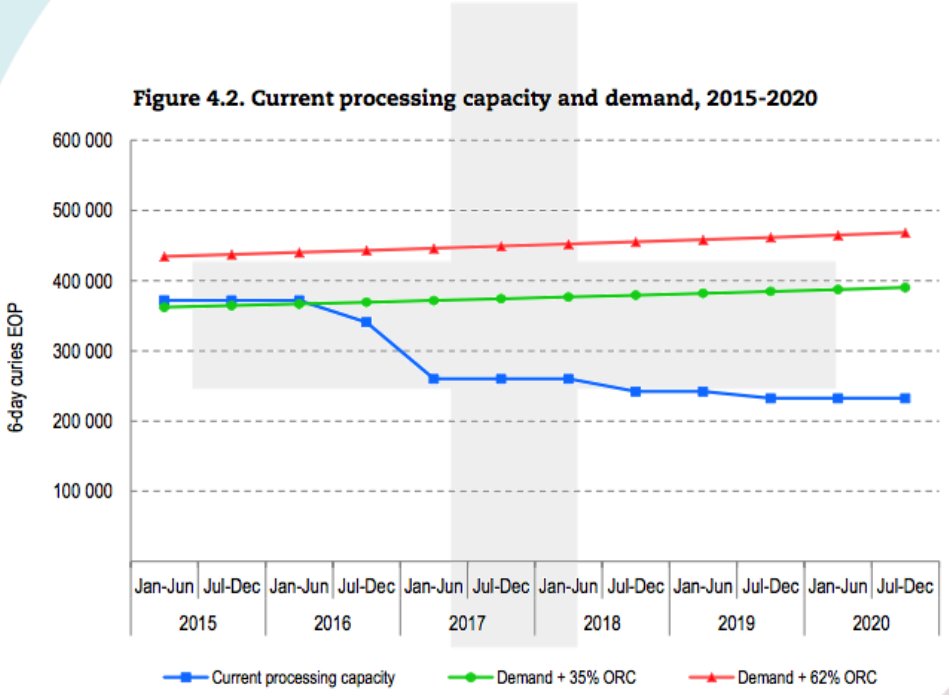
Sentinel Lymph Nodes

Radioisotope and blue dye injection

- Radioisotope has a 6-hour half-life meaning surgery is scheduled within 24-hours of injection
- Complex supply chain limits availability
- Radioactive tissue needs special disposal

Radioisotope Shortage

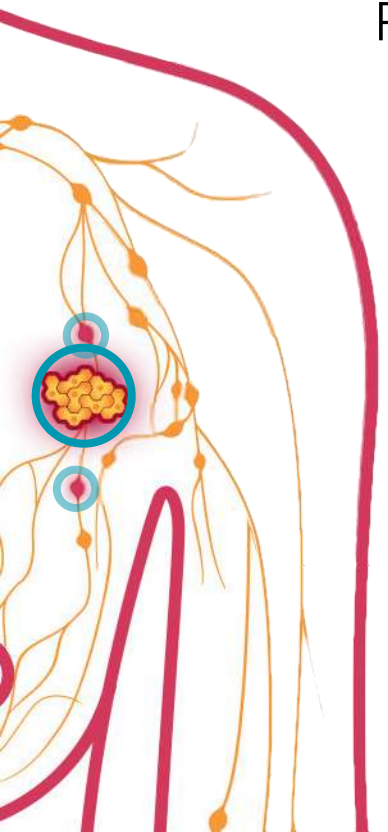
- Apr 2014 OECD Report on the supply of medical radioisotopes
- In Europe, processing capacity is particularly limited
- Global processing capacity is insufficient to ensure secure supply of $^{99}Mo/^{99m}Tc$ in the period through 2020



Endomag's Plan

- Replace the radioisotope-labelled colloid with a magnetic nanoparticle of similar dimensions
  - Removes a material with a half-life, improving availability and workflow
  - Reduces radioactivity from the OR and hospital waste stream
  - Provides the potential for a reliable and robust supply chain
- Replace the gamma-ray detection probe with a magnetic probe to locate the magnetic nanoparticles taken by the sentinel lymph nodes

Endomag's Solution



Primary Tumour

Magseed® placement located with Sentimag®

- Seed is firmly implanted into the tumour and doesn't move, helping to improve accuracy
- Allows the surgeon to pinpoint cancer and select the best cosmetic approach
- Magnetic seed can be implanted up to 30 days in advance improving workflow between radiology and surgery

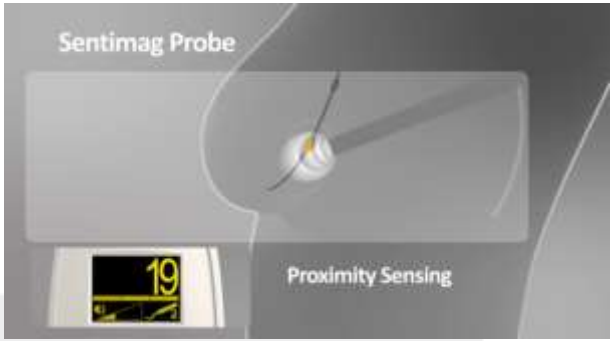
Sentinel Lymph Nodes

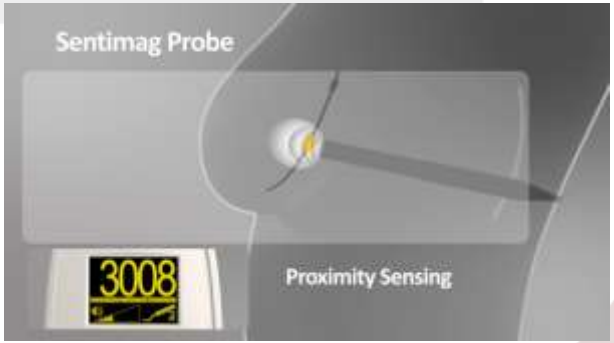
Sienna® injection located with Sentimag®

- Can be injected in the OR, eliminating pain
- Can be injected up to 7 days ahead of surgery for improved scheduling
- Removes radiation from OR and resolves availability
- Clinically proven to be as effective as current standard

Sentimag®

- Sentimag's handheld probe is directional, and indicates proximity by an increase in signal value and audio pitch
- Sentimag received CE mark approval in Dec 2010

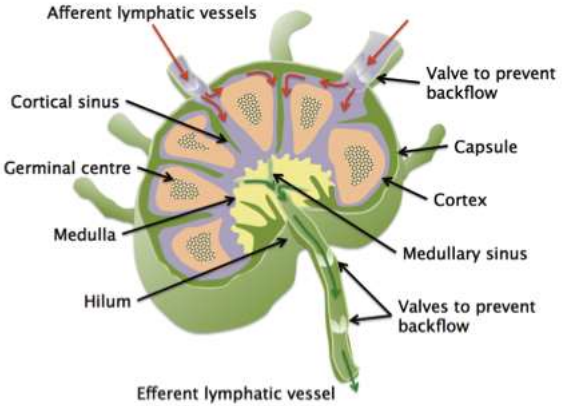


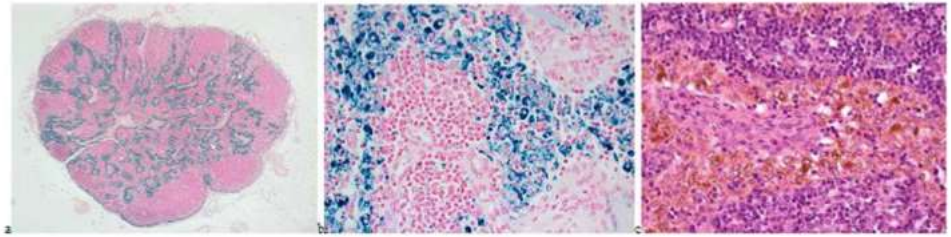


Early Development Crisis

- Iron oxide MRI contrast agents varied from market to market across the world
- More concerning was that iron oxide agents started disappearing from the market due to competition with gadolinium and, by Jan 2011, the only agent available in the EU was discontinued
- Endomag needed to develop something – quickly!
- **Bonus challenge**: all MRI contrast enhancement agents are regulated as drugs

What We Knew

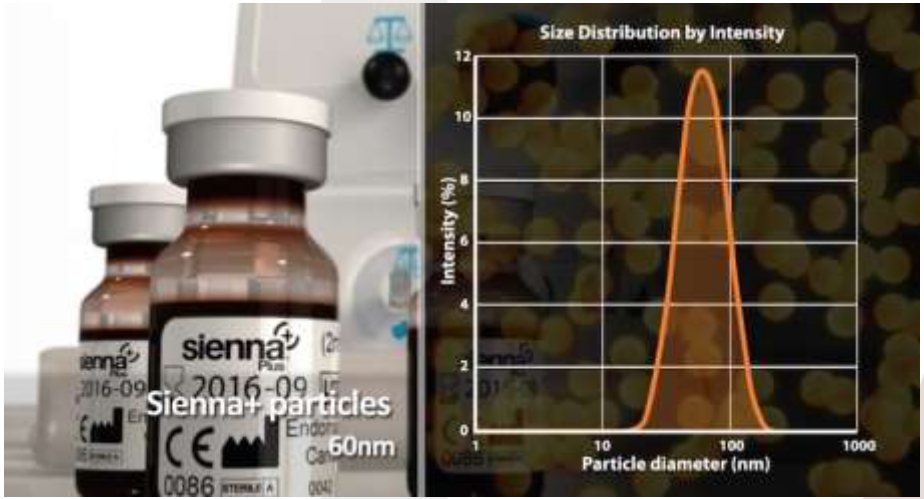




- Dextran-coated iron oxide nanoparticles were retained in the lymph node sinuses
- Particles didn't appear to transit to higher echelon nodes (~100nm diameter)
- But, the rate of transit to the first node was not ideal for impatient surgeons

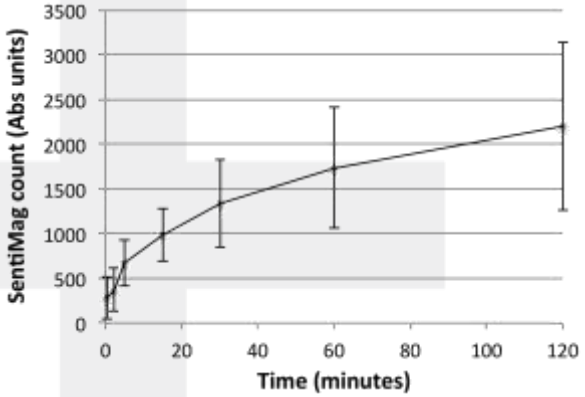
Nanoparticle Selection

- Endomag investigated lymph node sinus structure and identified an ideal diameter in the range of 40-80nm
- Mission was to develop or source a sub-22nm iron oxide particle with a biocompatible coating that increased its diameter to ~60nm
- Ultimately sourced a material that had a long safety history, but as an MRI contrast agent… a drug



Regulatory Challenges

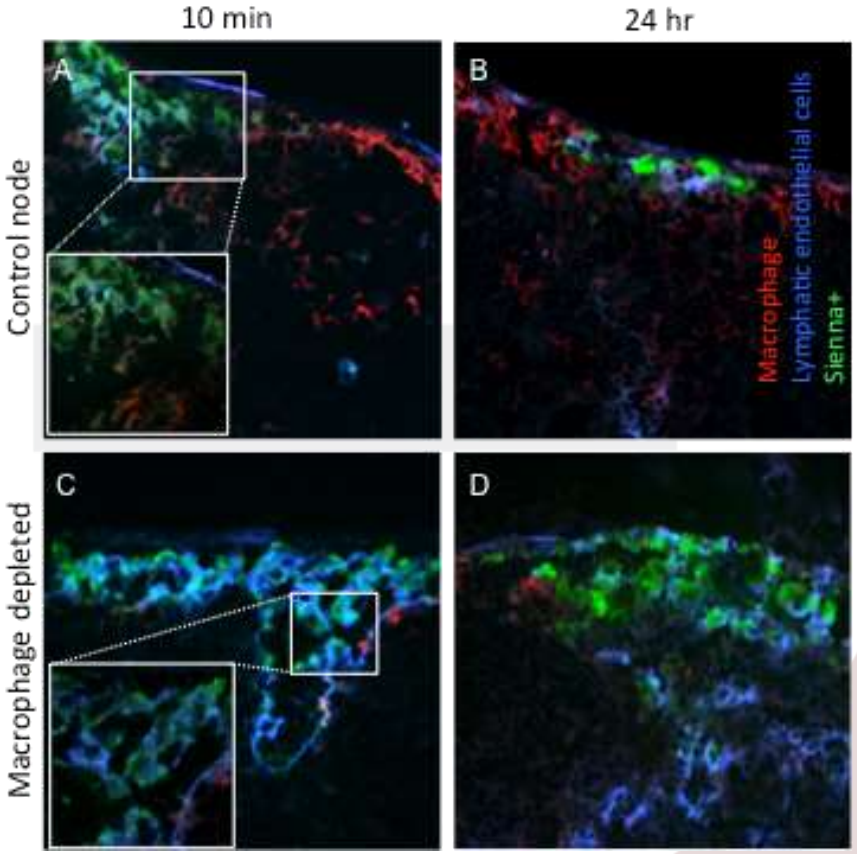
- All MRI contrast enhancement agents are regulated as drugs
- However, Article 1(2)(a) of the Medical Device Directive 93/42/EEC (MDD) suggested that Sienna could be classed as a medical device as it achieves its primary intended action without employing pharmacological, immunological or metabolic means
- Endomag initiated a pre-clinical investigation to evaluate the mechanism of transport and retention in the lymph node



Magnetic signal at draining lymph node vs time after injection of Sienna at the third inguinal papilla in a porcine model

Mechanism of Action

- Due to its particle size, Sienna+ is taken up into lymphatic vessels with the normal flow of lymph and flows to the lymph nodes
  - Pre-clinical and clinical studies showed transit to the node in minutes. Only free transport could account for this rapid uptake.
  - Cell trafficking experiments showed peripheral immune cells reaching the nodes only after a number of hours at the earliest.



Sienna+ Approval – Europe

- In Jul 2011, the MHRA agreed that Sienna could proceed for evaluation as a Class IIa medical device
- Successful formulation, manufacturing and technical file audit supported CE approval in Dec 2011 making Sienna the first marketed nanoparticle medical device

Sienna®

- Designed for sentinel node localisation
- Magnetic nanoparticles optimized for lymph node uptake regulated as a device
- Resolves availability of the standard of care
- Improves procedural convenience
- Puts the surgeon in control
- Over 30,000 breast cancer procedures performed
- FDA PMA approval expected Q2 2018*

CE

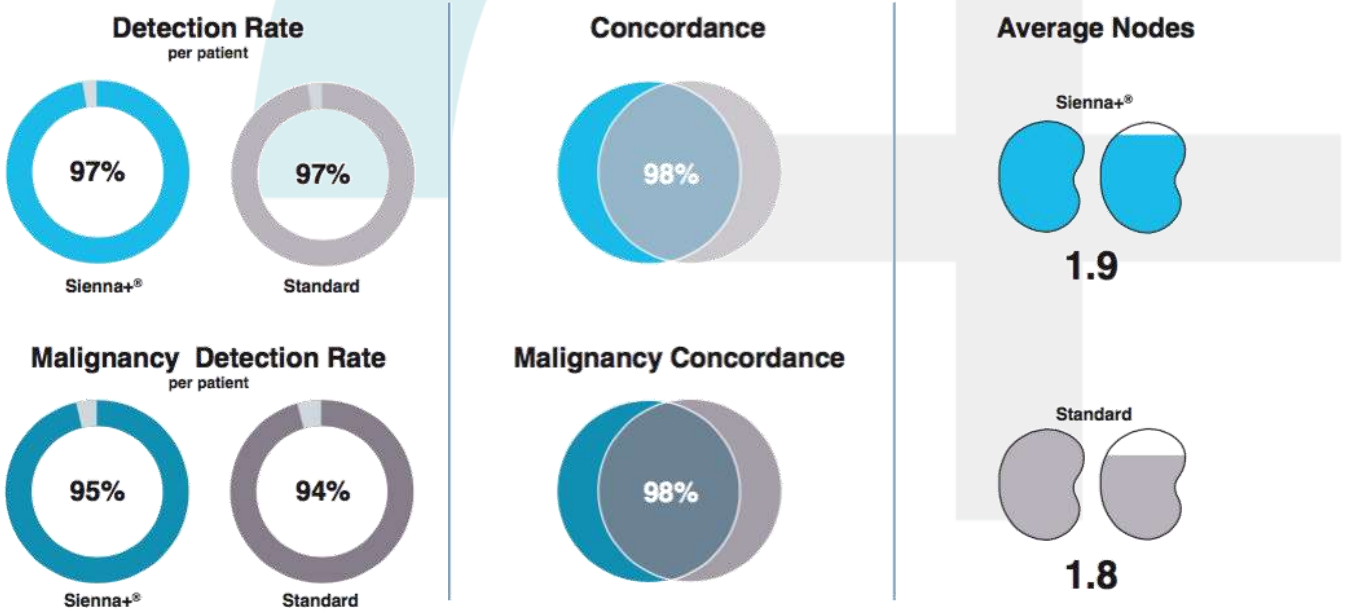
Health Canada Santé Canada

TGA Health Safety Regulation

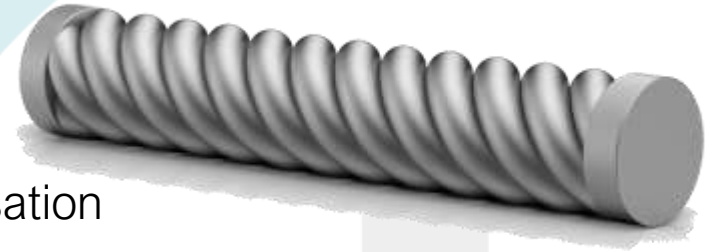
*Provisional approval received in Jun 2017 pending additional packaging validation and audits of the packager and Endomag

Clinical Evidence

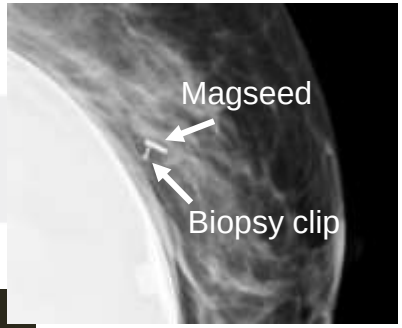
Results summary including >1,000 breast cancer patients across 7 trials



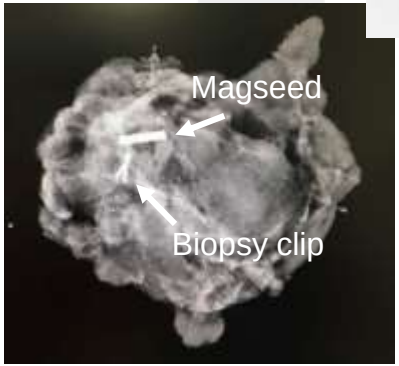
Magseed®



- Designed for impalpable lesion localisation
- Multi-mode detection: Sentimag, X-Ray and Ultrasound
- Improves the convenience and accuracy in impalpable lesion localisation and excision



Mammogram



Excised lesion

CE FDA 510(k) TGA Health Safety Regulation Health Canada Santé Canada

Epilogue

Leica BIOSYSTEMS North America (Jul 2016)

sysmex EMEA (Feb 2013)

- Headquartered in Cambridge, UK after spinning out from University College London and the University of Houston in 2007
- Platform launched in Europe in February 2013, with expansion into the US market in mid-2016
- 2017 revenues of £4m via strategic distribution partnerships – 256% YoY growth from 2016
- Treated >30,000 breast cancer patients across 30 countries since platform launched

Regulatory Changes

- In May 2017, the new Medical Device Regulation (MDR) was published, starting a 3-year transition from the Medical Device Directive (MDD)
- There is a “grace period” through to May 2022 for medical devices, but substantial changes won’t be allowed
- How does the MDR impact nanomedicine?

  Rule 19

  All devices incorporating or consisting of nanomaterial are classified as:

  - class III if they present a high or medium potential for internal exposure
  - class IIb if they present a low potential for internal exposure; and
  - class IIa if they present a negligible potential for internal exposure

Thank You