endomag

Taking a nanoparticle medical product into the global market

July 29th 2021

Agenda

- Endomag overview
- Crash course in (nano)magnetism
- An unmet need in breast cancer surgery
- Endomag’s solution
- Challenges in clinical translation
- Upcoming challenges

Endomag Overview

Endomag helps cancer patients by:

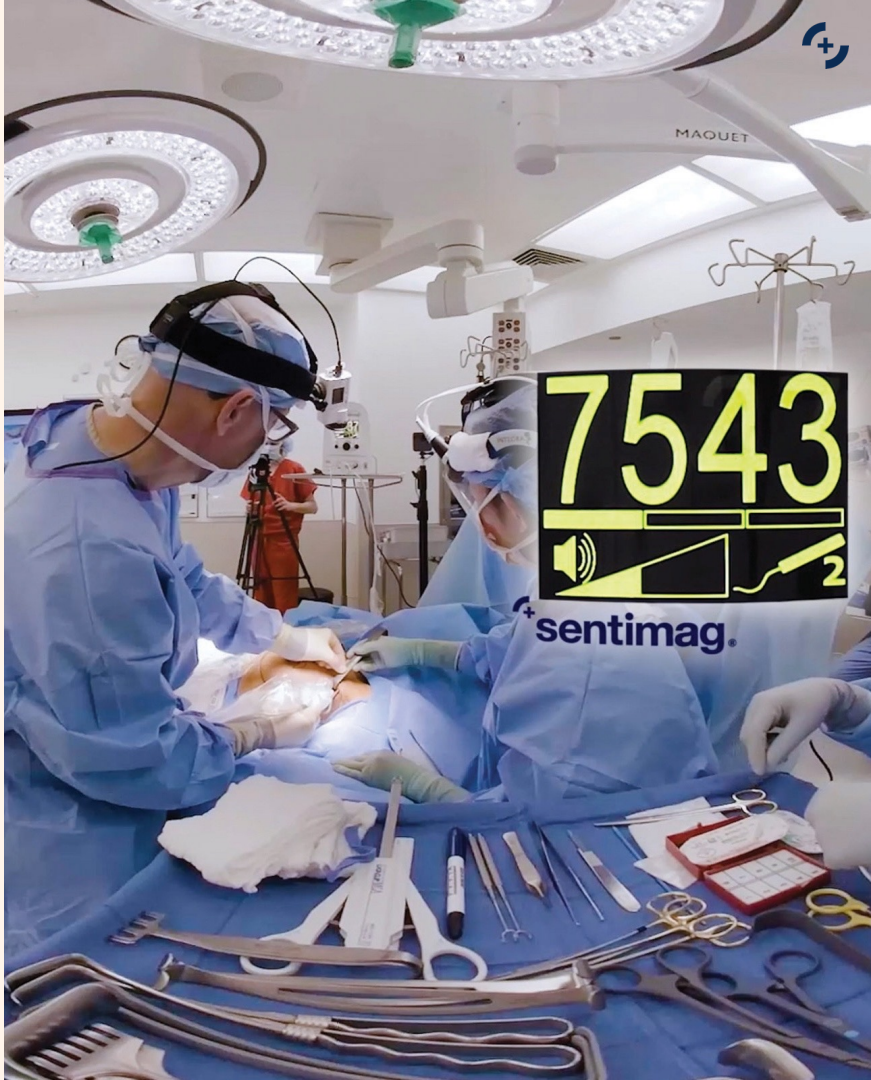
preventing unnecessary surgery

improving outcomes and patient experience when surgery's needed

increasing access for all in need

Market Focus

- Breast cancer is the most commonly occurring cancer worldwide with **2.3m cases annually** and the leading cause of cancer death in women[1]
- Global incidence is projected to reach **3.0m by 2040** due to continued demographic changes
- Our global addressable market in oncology is **£2B+**



[1]World Health Organization's International Agency for Research on Cancer (IARC) GLOBOCAN 2020 database

Company Profile

- Formed from a collaboration between the **University College London (UCL)** and the **University of Houston**, and initially funded by **Innovate UK**
- Leading body of peer-reviewed data supporting use and clinical benefit from an international base of KOLs
- Award winning and rapidly growing:
  - Double Queen's Award winner – 2018 Innovation and 2021 International Trade
  - 63rd in the Sunday Times' Tech Track 100 in 2019, and 43rd in 2020
  - 2021 Financial Times' "FT 1000" list of the fastest growing European companies (7th highest growth healthcare company)

Current Products

Magseed®

Designed for lesion localisation and used in over 85,000 cases

Magtrace®

The world's most flexible tracer for staging breast cancer used in over 75,000 cases

Where are we now?

160,000+ patients

Benefited from the Magtrace® or Magseed® markers since they were approved in 2012 & 2016 respectively

600+ hospitals

Our Sentimag® system is in use in over 600 hospitals worldwide

43+ countries

While our primary territories are the US & EMEA, we are working towards addressing new countries

Magnetism Crash Course

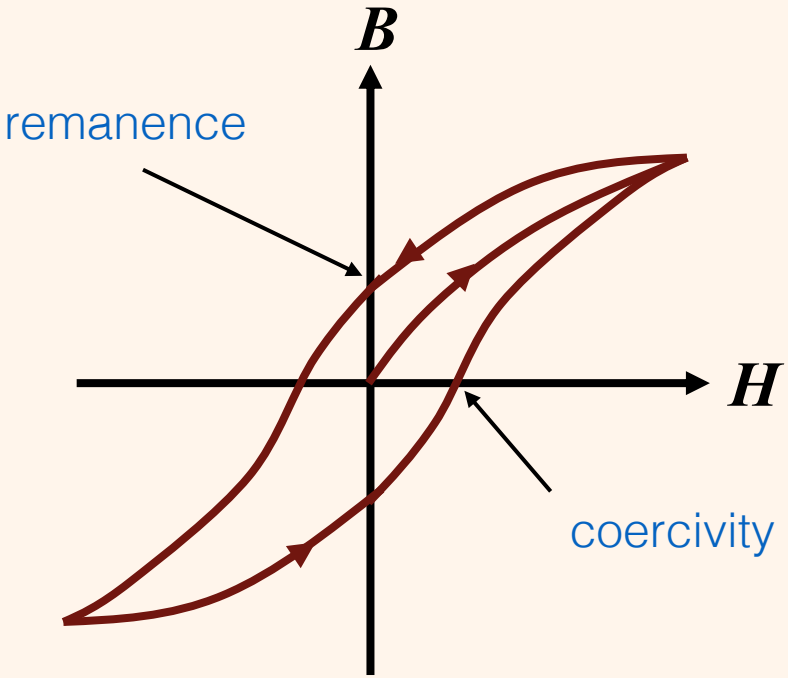
Magnetic Terms

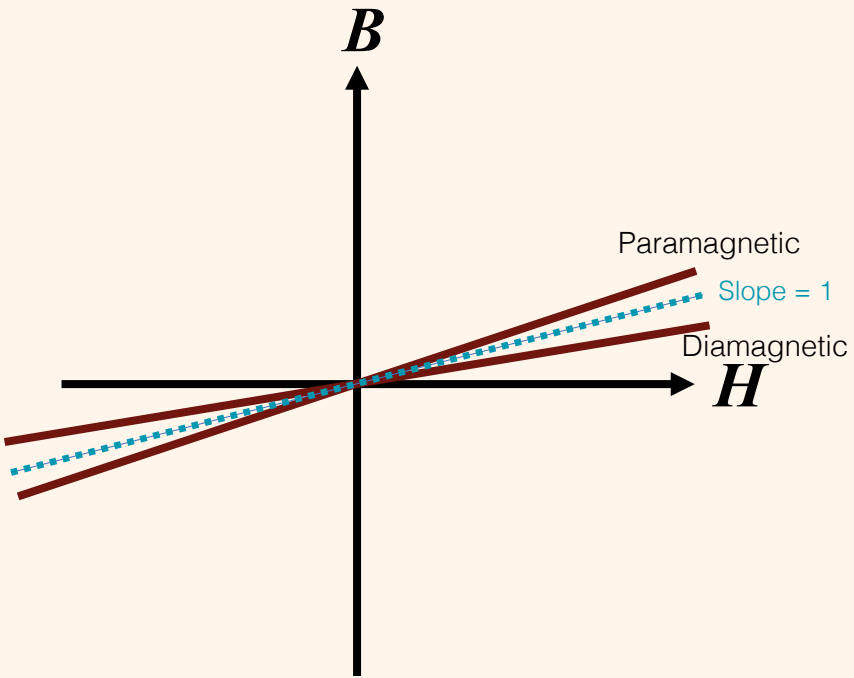
Magnetism in materials arises from the configuration of spin magnetic moments from their constituent electrons

Type	Cartoon	Alignment
Ferromagnetism		All spins aligned and parallel
Ferrimagnetism		Most spins aligned and parallel
Antiferromagnetism		Alternating alignment in spins resulting in net zero magnetisation
Paramagnetism		Spins randomly oriented until an external field is applied, spins aligning parallel
Diamagnetism		Null spins until an external field is applied, spins aligning antiparallel

Magnetic Behaviour

Ferro- or ferrimagnetic behaviour



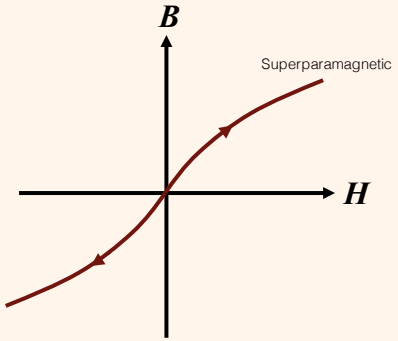


Nanoscale Magnetic Particles

- As ferro- or ferrimagnetic particles transit the nanoscale, they reach a point where magnetisation randomly changes direction due to thermal energy
- While these particles behave similarly to paramagnets, they also exhibit very high magnetic susceptibility – they are termed ‘superparamagnetic’
- Superparamagnetic volume can be derived as:

$$V_{sp} < 25kT/K$$

k is Boltzmann’s constant
T is Temperature
K is magnetocrystalline anisotropy

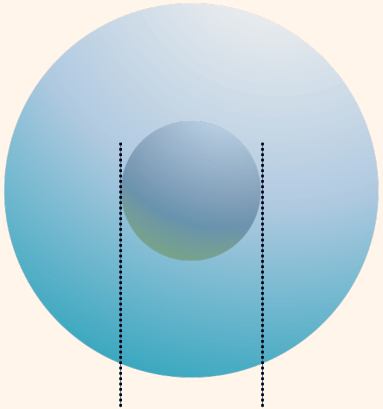


- For magnetite at room temperature, $V_{sp} < 5.7 \times 10^{-18}$ cm^3 or a diameter of < 22 nm

Considerations for Nanomedicine

- Ferromagnetic nanoparticles exhibit remnant magnetism that could cause them to stick together - **dangerous *in vivo***
- Superparamagnetic nanoparticles have zero remanence, but high susceptibility
- While a range of materials exhibits superparamagnetism at the nanoscale, iron oxide is well tolerated *in vivo*

Iron oxide nanoparticle with hydrophilic, biocompatible coating



D_{sp} < 22 nm

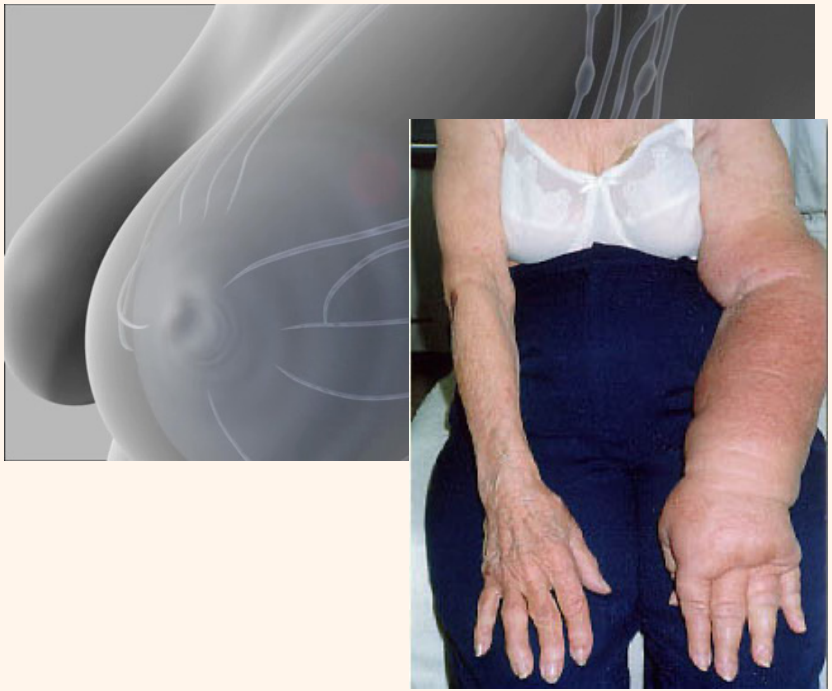
The Unmet Need

Breast Cancer

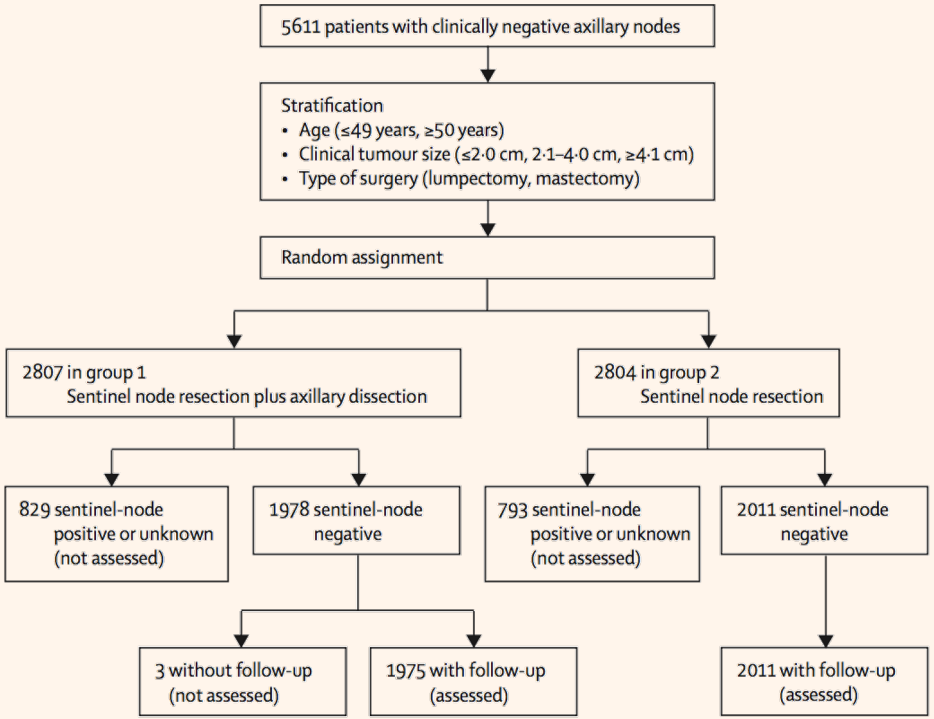
- The global incidence of breast cancer is 2.3m annually and is the leading cause of cancer death in women
- Breast cancer incidence is projected to reach 3.0m by 2040 due to continued demographic changes
- When cancer is confirmed, it's 'stage' must be established to decide next-steps for treatment – $T_{1-4}N_{0-3}M_{0-1}$ system (Tumour, Nodes, Metastasis)
- Sentinel lymph node biopsy (SLNB) is the gold standard for staging nodes
- However, only 1 in 6 patients globally receives the gold-standard of care

Axillary Lymph Node Dissection (ALND)

- When a tumour spreads, its cells are carried away by the interstitial fluid of the lymphatic system
- Axillary lymph node dissection (ALND) was the original surgical method for determining whether cancer had spread
- Around 30 lymph nodes were surgically removed for histological examination

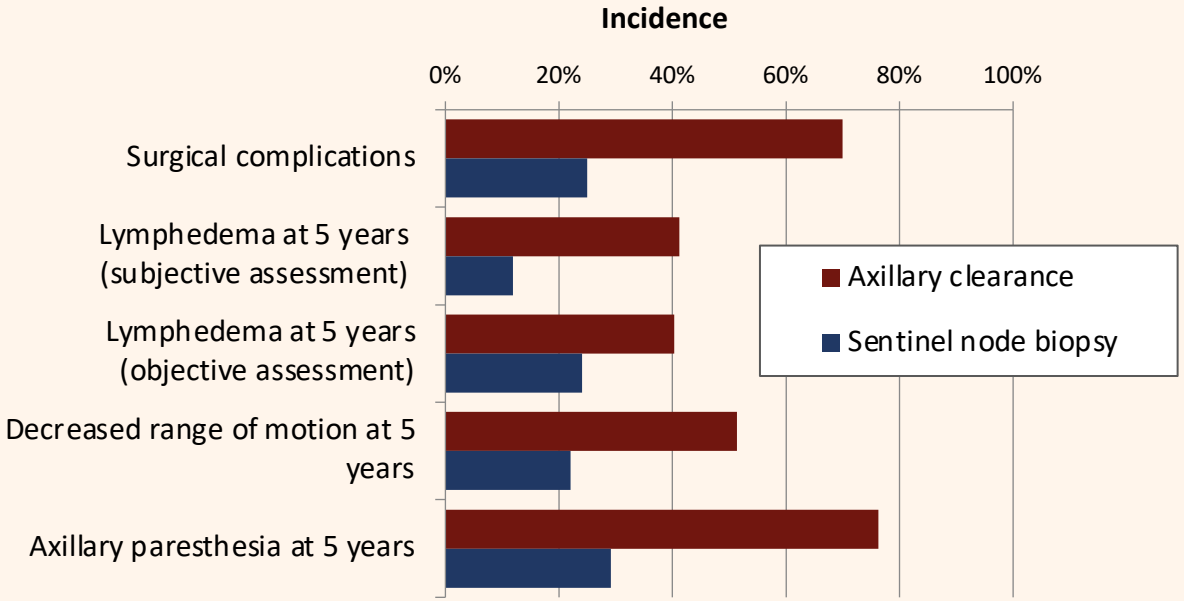


NSABP B-32 Trial (May 1999 to Feb 2004)



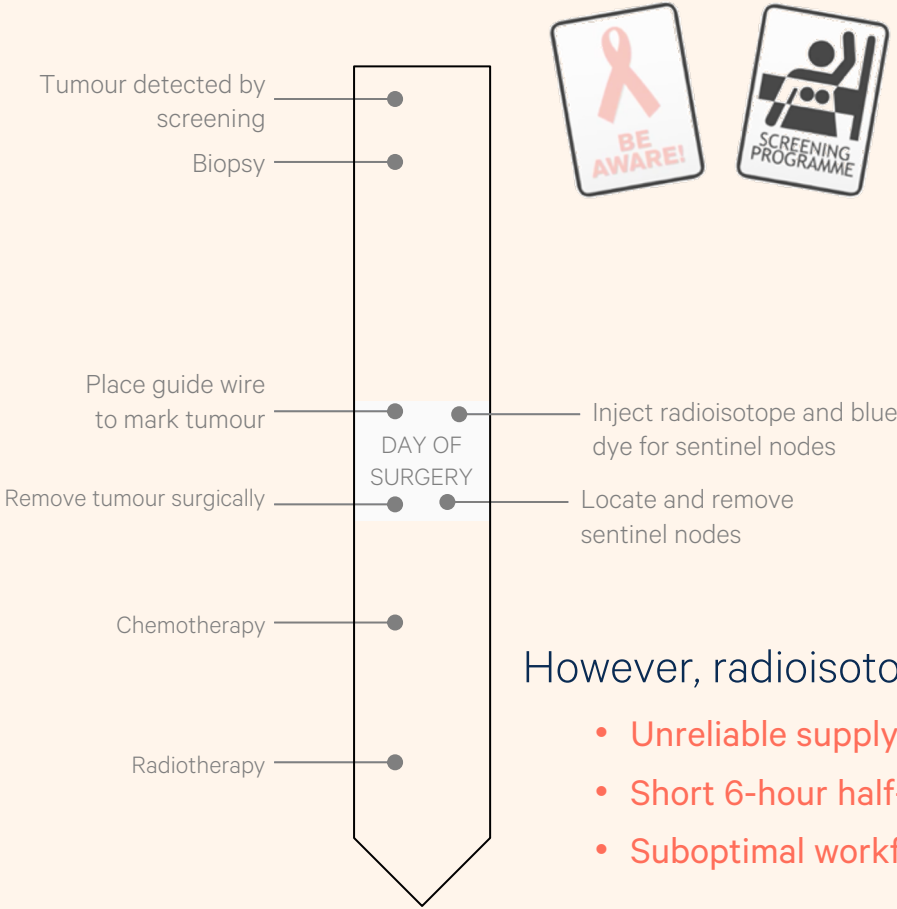
- A sentinel lymph node biopsy (SLNB) is where only 1-2 lymph nodes are removed and analysed
- **The Lancet, October 2010:** Results from 5,611 women across 80 North American institutions
- Confirmed equivalent survivability at 5 years between patients with SLNB and those with ALND – established SLNB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

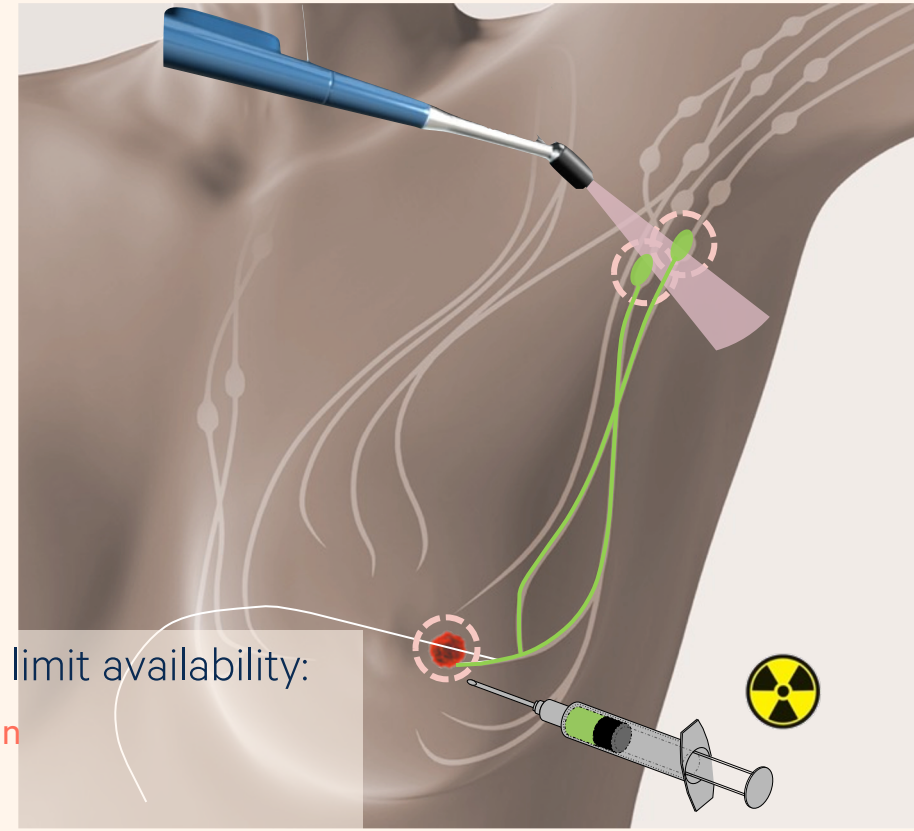
SLNB is superior for patients



- Surgical complications including wound infections and seromas greatly reduced with SLNB versus axillary clearance[2]
- Key measures of morbidity five years after surgery also all significantly lower for SLNB[3]

2. Lucci, A, et al. Surgical Complications Associated With Sentinel Lymph Node Dissection (SLND) Plus Axillary Lymph Node Dissection Compared With SLND Alone in the American College of Surgeons Oncology Group Trial Z0011, JCO August 20, 2007 vol. 25 no. 24 3657-3663
3. Teshome M, Ballman KV, McCall LM, et al: Long-term incidence of lymphedema after sentinel lymph node dissection for early stage breast cancer: ACOSOG Z0010 (Alliance). 2014 SSO Cancer Symposium.



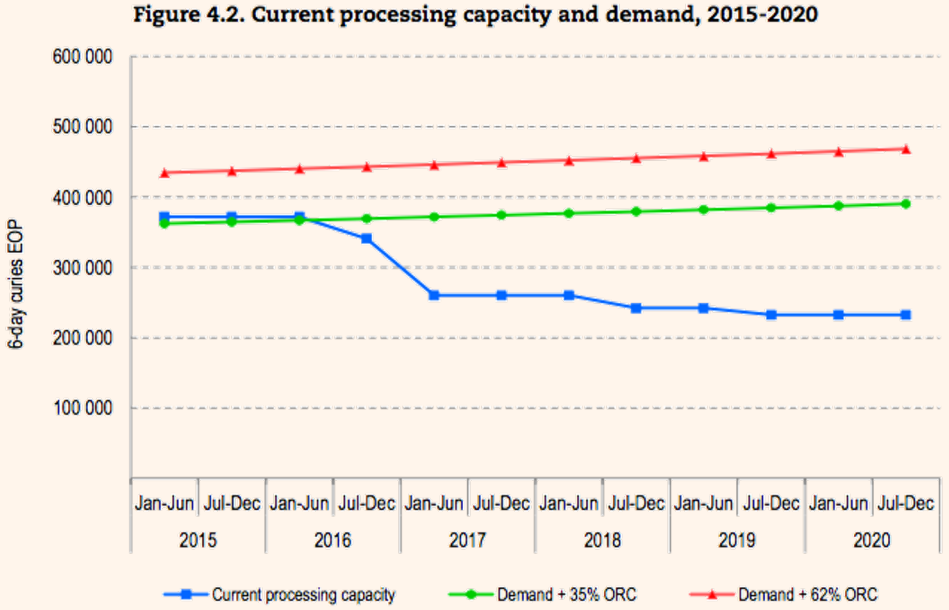


However, radioisotopes limit availability:

- Unreliable supply chain
- Short 6-hour half-life
- Suboptimal workflow

Radioisotope Shortage

- April 2014 OECD Report on the supply of medical radioisotopes
- In Europe, processing capacity is particularly limited
- Global processing capacity is challenged to ensure secure supply of $^{99}Mo/^{99m}Tc$



Endomag's Solution

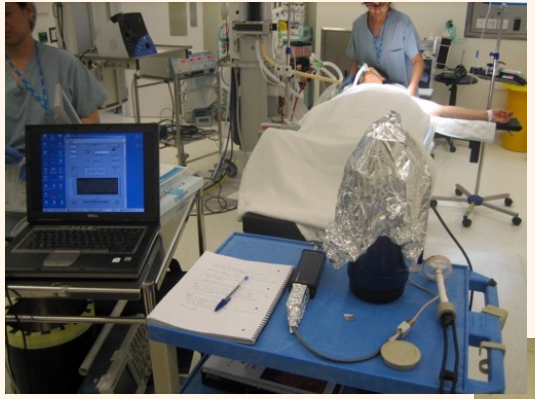
The Concept

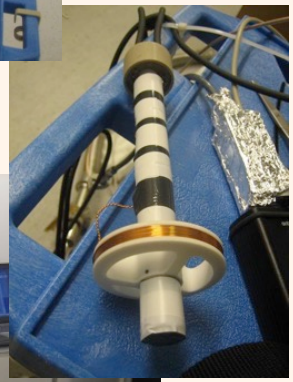
- Replace the radioisotope-labelled colloid and blue dye with a magnetic nanoparticle of similar dimensions
  - Removes a material with a half-life, improving availability and workflow
  - Reduces radioactivity from the OR and hospital waste stream
  - Provides the potential for a reliable and robust supply chain

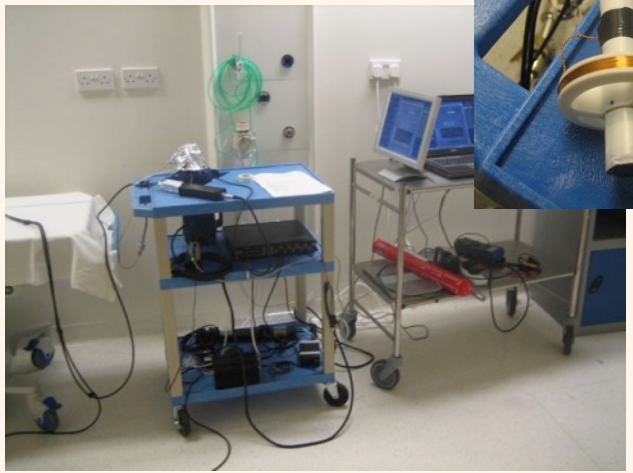
- Replace the gamma-ray detection probe with a magnetic probe to locate the magnetic nanoparticles taken by the sentinel lymph nodes

System Requirements

- **Our target:** To meet the clinical need, we needed to detect 100 µg of a magnetic tracer at a distance of 20 mm from the tip of a hand-held probe
- **Our calculations:** We required a stimulated response (susceptometry), and the ability to discern a 60 pT change on top of a magnetising field of 50 µT – **a 1 ppm challenge**

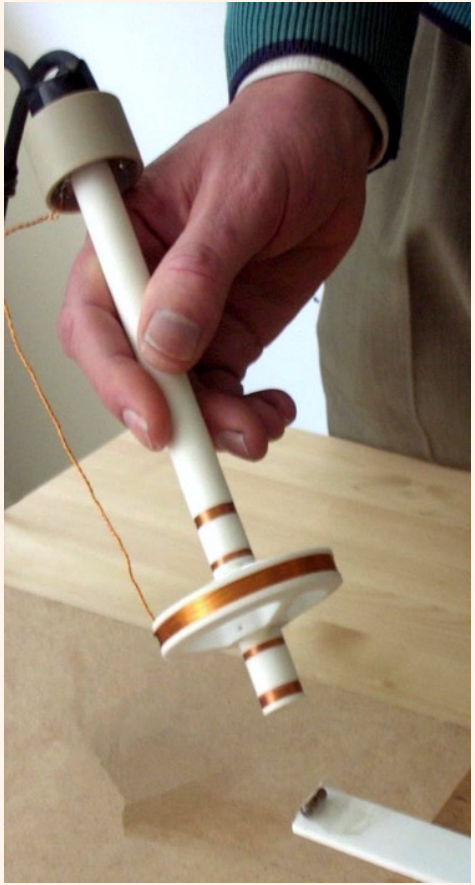






Engineering Innovation

- **2004 to 2007:**
  - Selected a SQUID detector, so focused on noise reduction in the sense coils, probe, cables and electronics
  - Based on current transduction
  - Nested gradiometer sense coil design
  - Developed novel electronics to limit the mechanical and thermal sources of noise
  - However, the SQUID required cryogenic cooling

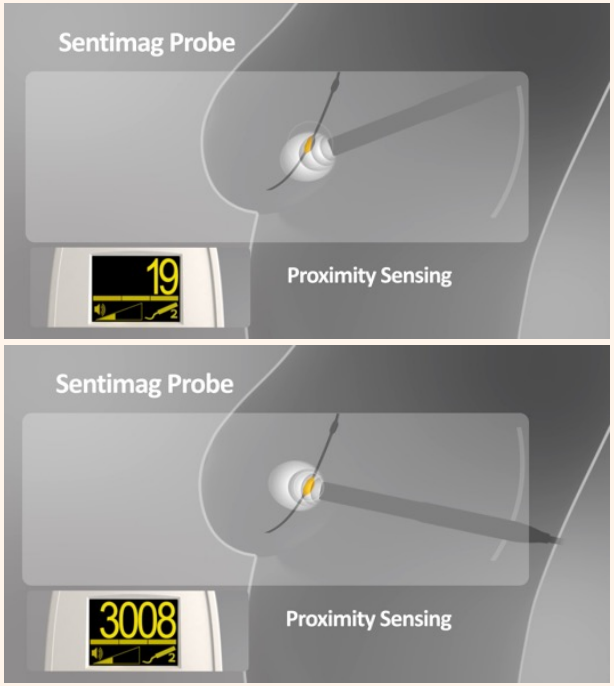


Engineering Innovation

- **2008 to 2010:**
  - Made the leap to a non-cryogenic system
  - Based on voltage transduction
  - Using best available operational amplifier in a voltage detection circuit
  - Boosted signal by increasing the number of sense coil turns and the drive frequency
  - **CE mark awarded in December 2010**, and initially planned to use in combination with an iron oxide MRI contrast agent, off-label

Sentimag®

The probe is directional, and indicates proximity by an increase in signal value and audio pitch



Patient presents with tumor

Biopsy

Place Magseed to mark tumour

Inject Magtrace for sentinel nodes

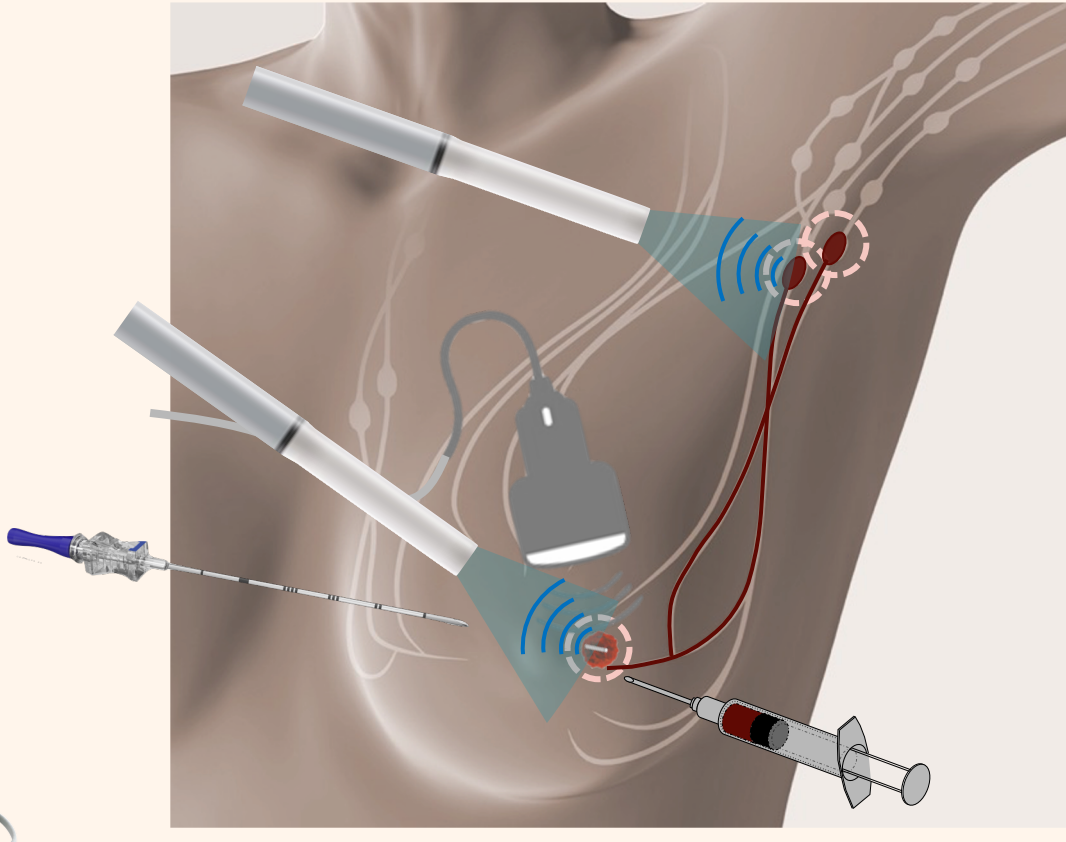
DAY OF SURGERY

Locate and remove sentinel nodes

Remove tumour surgically

Chemotherapy

Radiotherapy



Clinical Translation Challenges

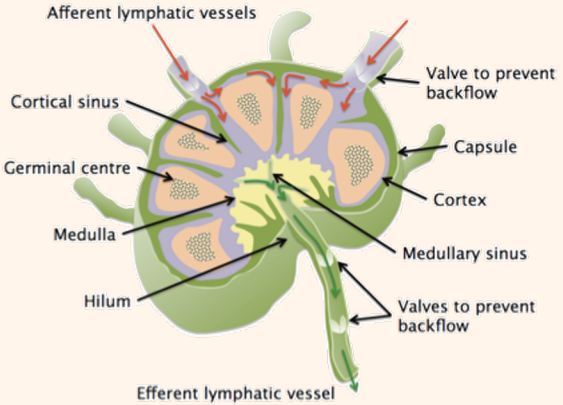
Early Development Crisis

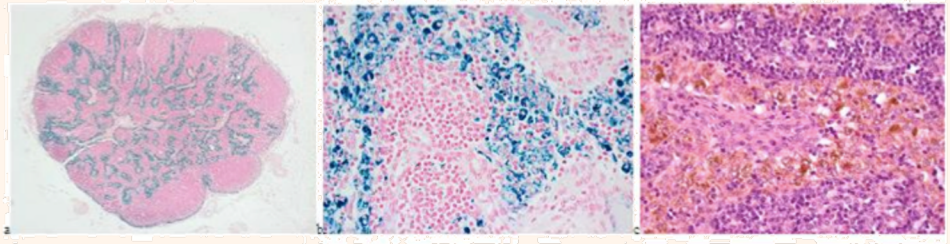
- Iron oxide MRI contrast agents varied from market to market across the world
- More concerning was that iron oxide agents started disappearing from the market due to competition with gadolinium and, by January 2011, the only agent available in the EU was discontinued
- Endomag needed to develop something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

Specification Development

- Safe
  - Minimal toxicity and clear degradation pathway
  - Avoids embolism
- Best Performance
  - High magnetic susceptibility
  - Appropriate size – retained in the sentinel node, but rapid transit to them
- Quick to Market
  - Ready supply chain
  - Regulatory efficiency

What We Knew

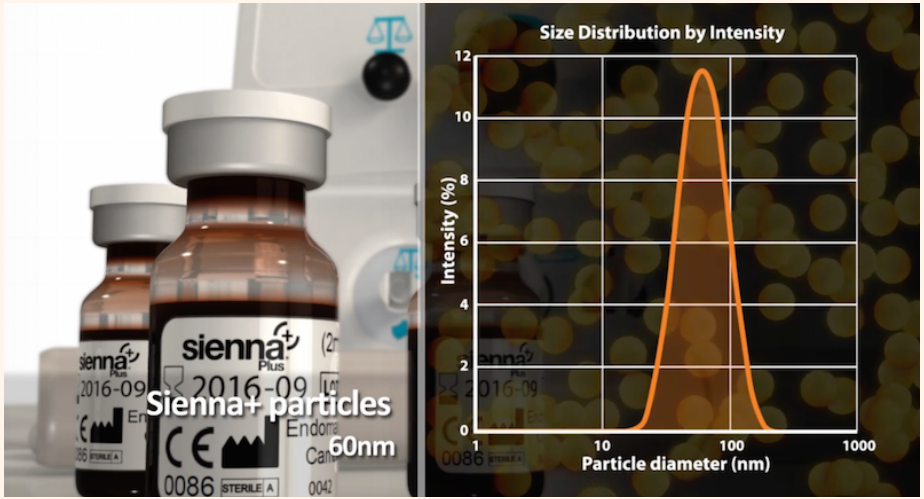




- Dextran-coated iron oxide nanoparticles were retained in the lymph node sinuses
- Particles didn't appear to transit to higher echelon nodes (~100nm diameter)
- But the rate of transit to the first node was not ideal for impatient surgeons

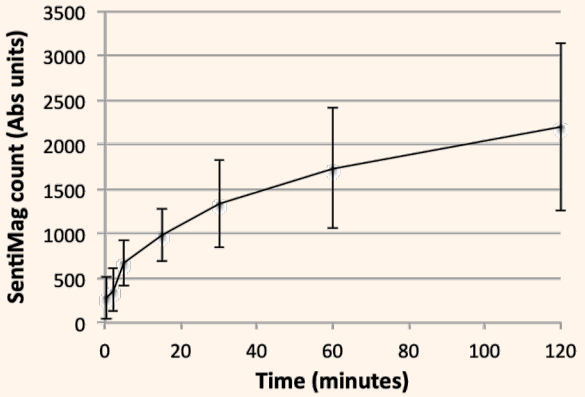
Nanoparticle Selection

- 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 Clarity?

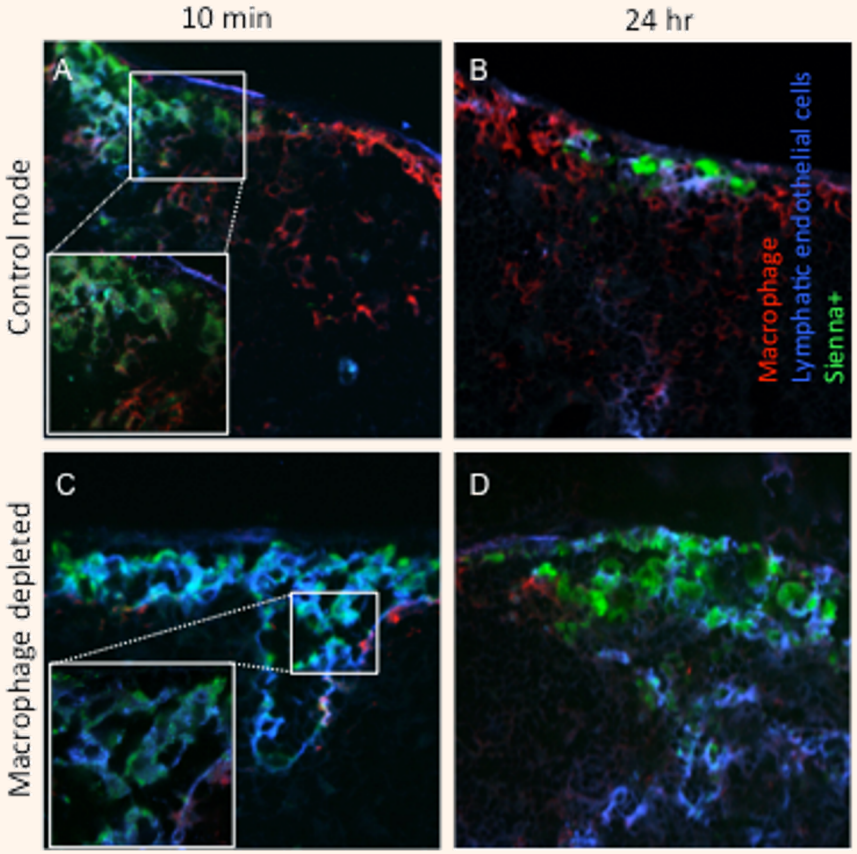
- All MRI contrast enhancement agents are regulated as drugs
- However, Article 1(2)(a) of the Medical Device Directive 93/42/EEC (MDD) suggested that our “Sienna+” could be classed as a medical device as it achieves its primary intended action without employing pharmacological, immunological or metabolic 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

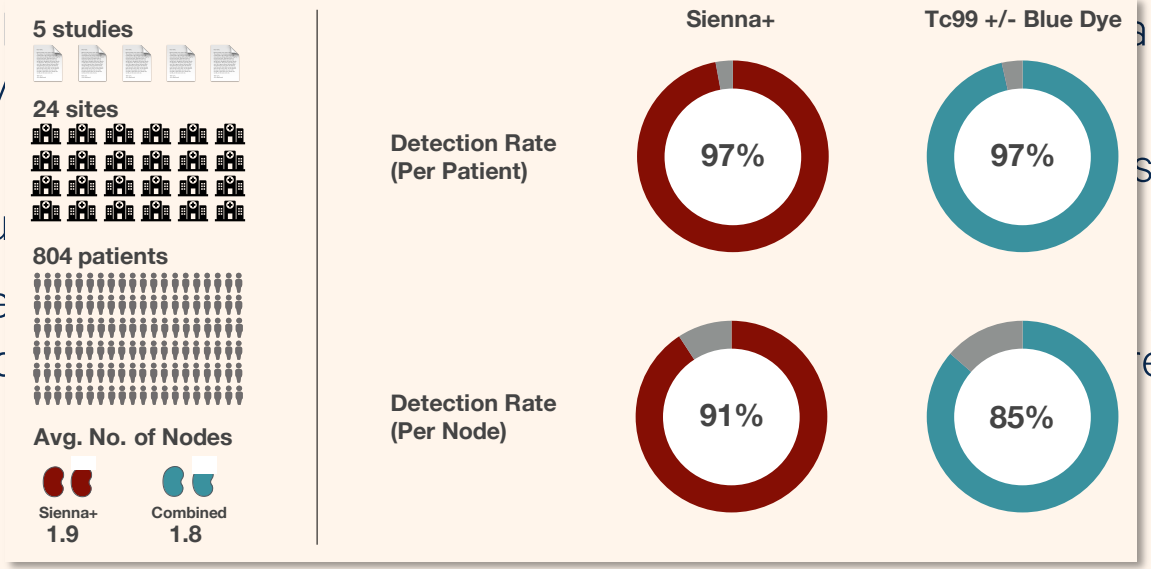
Mechanism of Action

- Due to its particle size, Sienna+ was taken into lymphatic vessels with the normal flow of lymph that flows to the lymph nodes
  - Pre-clinical and clinical studies showed transit to the node in minutes; and 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

- In July 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
  medical dev
- In 2012, the
  blue dye lau
- In subseque
  patients anc



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Magtrace® Approval

- In September 2013, the FDA also accepted a device primary mode of action, paving the route to an Investigational Device Exemption (IDE) and a multi-site pivotal trial that started in January 2015
- The ”SentimagIC” trial completed with 160 patients across six sites in December 2015 and met the primary endpoint of non-inferiority to the standard “combined” technique
- In July 2018, the FDA’s CDRH, in consultation with the Centre for Drug Evaluation and Research and support from the FDA’s Oncology Center of Excellence, approved the PMA for Sienna+ under a new name, Magtrace®
  … **but limited to mastectomy patients only**

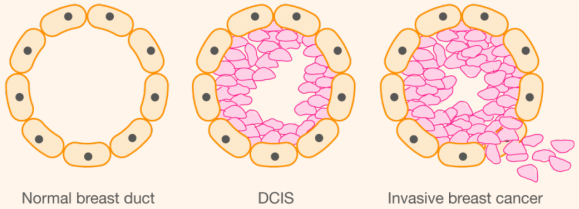
Upcoming Challenges

Extension of Label

- The 2018 PMA was limited to use only in mastectomy patients due to concerns over residual Magtrace and its potential to complicate MR imaging of possible recurrent disease
- Endomag has sponsored additional trials to confirm:
  - The time for residual degradation of Magtrace following surgery
  - The extent of complications using MRI with and without Gd contrast
  - The feasibility of using alternative imaging techniques for potential recurrent disease
- A PMA supplement to extend to all breast surgery procedures is currently under review with the FDA

New Techniques

- A delayed sentinel lymph node biopsy or “**dSLNB**” is an entirely new technique that was enabled by Magtrace thanks to its long residence time



- Concurrent SLNB is recommended for ductal carcinoma *in situ* (DCIS) patients having a mastectomy as it is difficult to perform a SLNB afterwards
- But only ~20% of DCIS patients are upgraded to invasive breast cancer diagnosis following pathologic staging
- That means around 80% of DCIS patients are having an unnecessary surgery
- **As its performance doesn’t degrade for weeks, Magtrace makes it simple to perform a SLNB afterwards saving patients from unnecessary surgery**

New Regulations

- In May 2017, the new Medical Device Regulation (MDR) was published, starting a 3-year transition from the Medical Device Directive (MDD)
- Given the Covid-19 pandemic, the deadline for compliance with MDR 2017/745 was extended to May 26, 2021
- There is a “grace period” through to May 2024 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

For any further questions,

please get in touch:

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