Commercialisation of nanomaterials: process, issues, and management
June 7, 2017

endomag

Taking a nano-based medical product to the international market

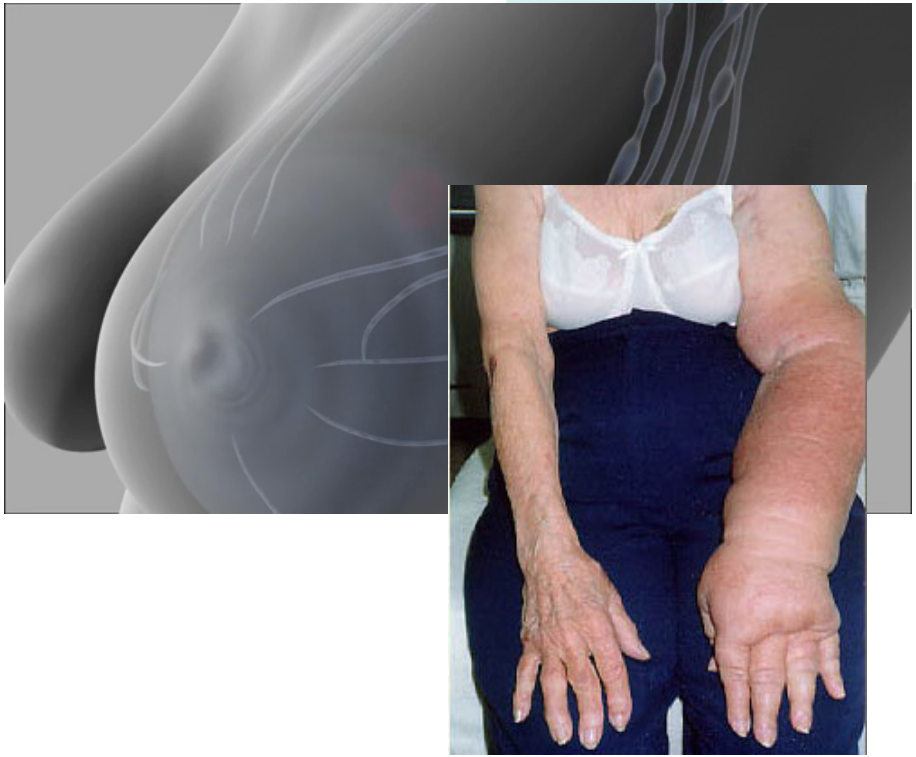
ISO 13485: 2003
MD 589249

The Unmet 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

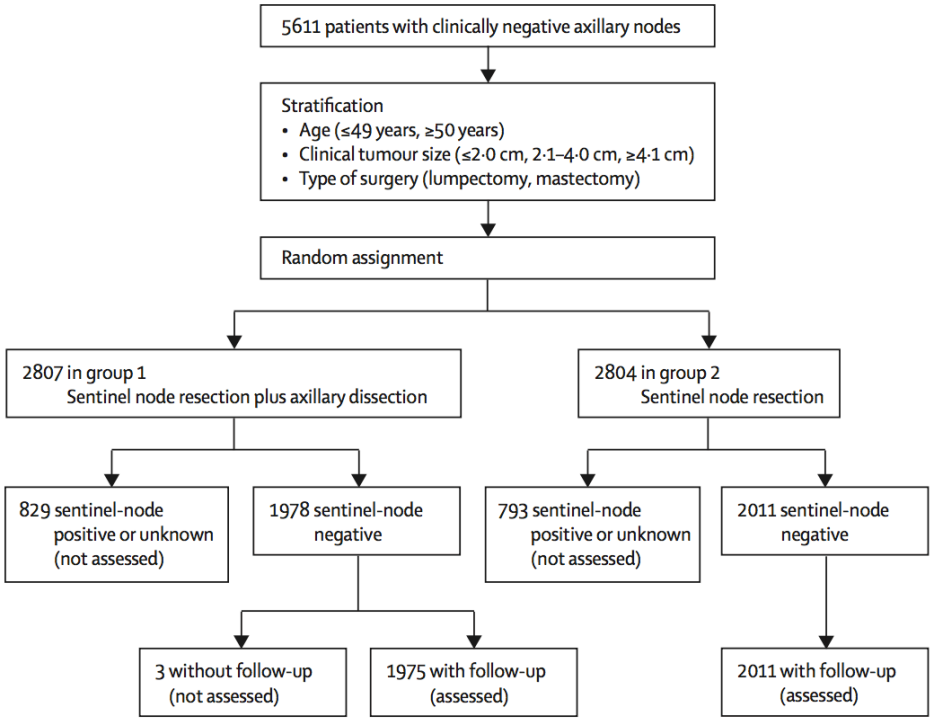
**Ginsburg, O. et al. The global burden of women's cancers. The Lancet (2016). doi:10.1016/S0140-6736(16)31392-7*

Breast Cancer and Lymphatics



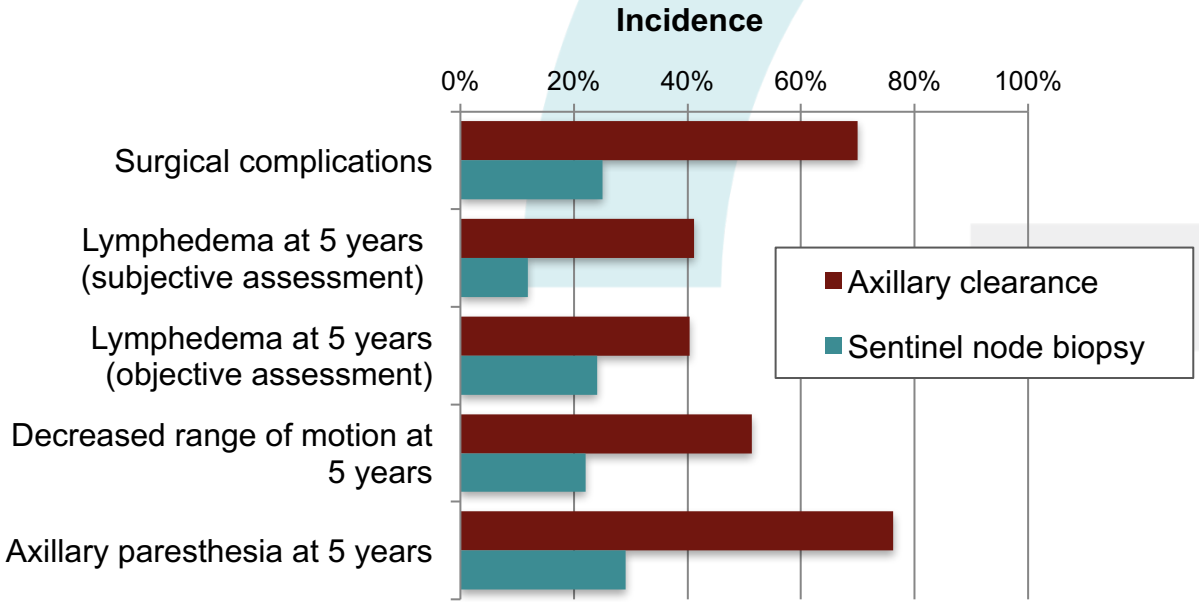
- When a tumour spreads, its cells are carried away by the interstitial fluid of the lymphatic system
- Axillary lymph node dissection (ALND) was the original surgical method for determining whether cancer had spread
- Around 30 lymph nodes were surgically removed for histological examination

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

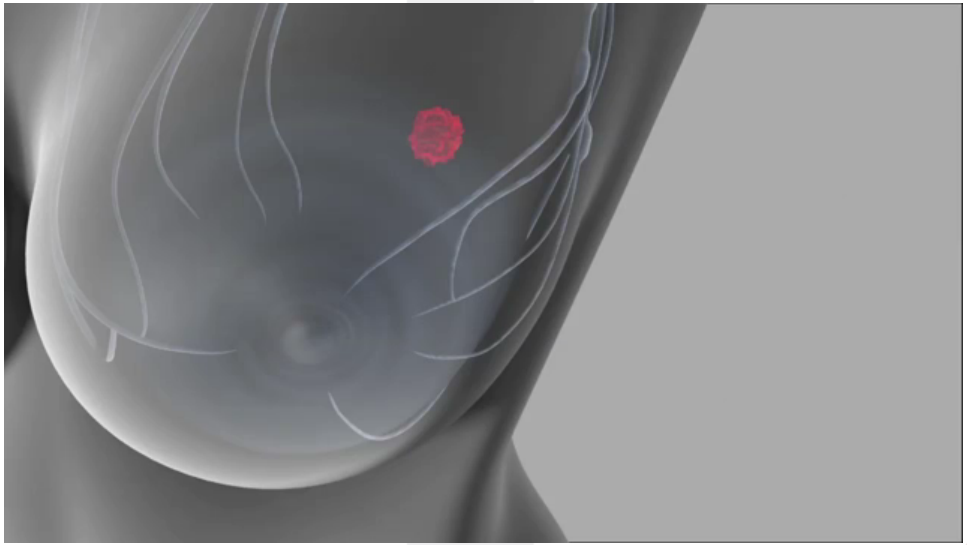


- Surgical complications including wound infections and seromas greatly reduced with SLNB versus axillary clearance[1]
- Key measures of morbidity five years after surgery also all significantly lower for SLNB[2]

1. 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
2. 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.

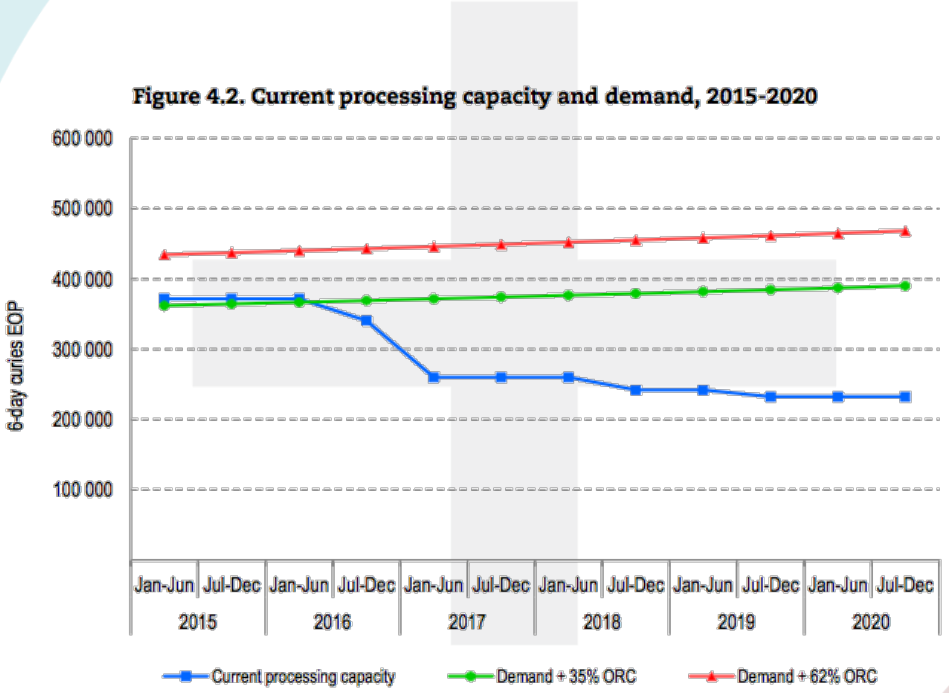
The Availability Issue

- The traditional technique injects a radioisotope that is filtered out by the node, and then located using a gamma-ray detecting probe
- However, radioisotopes limit availability:
  - Unreliable supply chain
  - Short 6-hour half-life
  - Suboptimal workflow



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



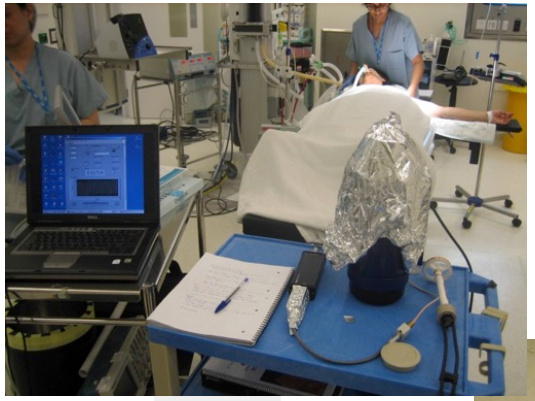
Endomag's Plan

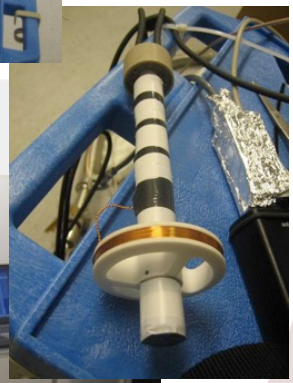
- Replace the radioisotope-labelled colloid with a magnetic nanoparticle of similar dimensions
  - Removes a material with a half-life, improving availability and workflow
  - Reduces radioactivity from the OR and hospital waste stream
  - Provides the potential for a reliable and robust supply chain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

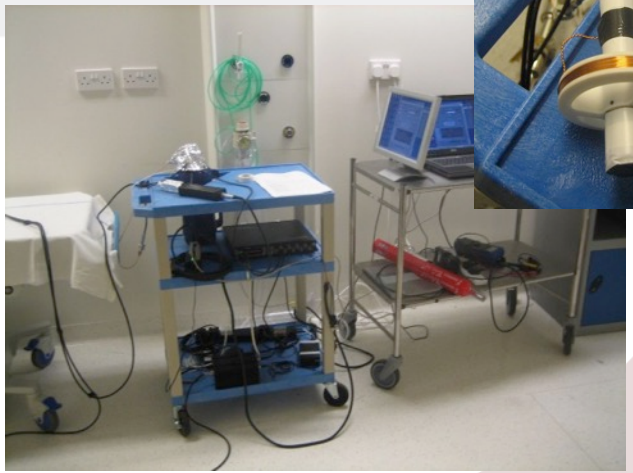
System Requirements

- **Our target:** To meet the clinical need, we needed to detect 100 µg of a nanoparticulate 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

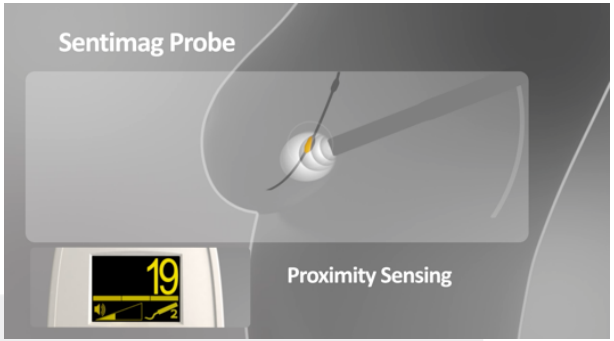


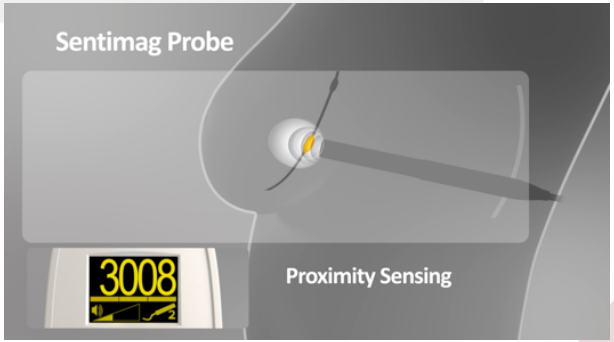




Sentimag®

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

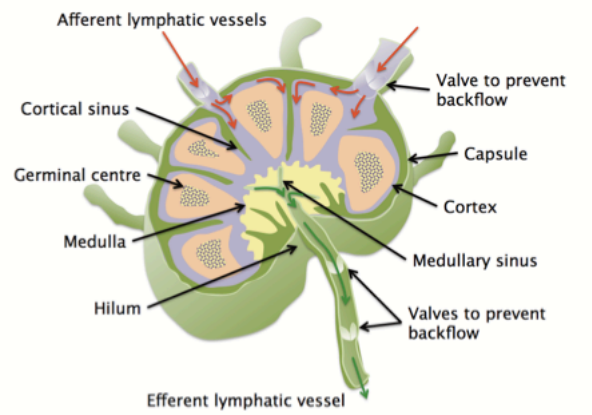


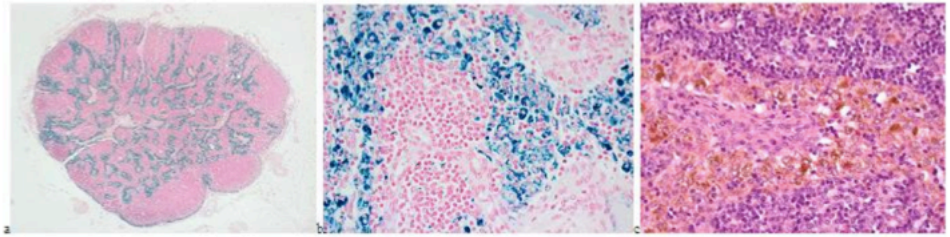


Early Development Crisis

- 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

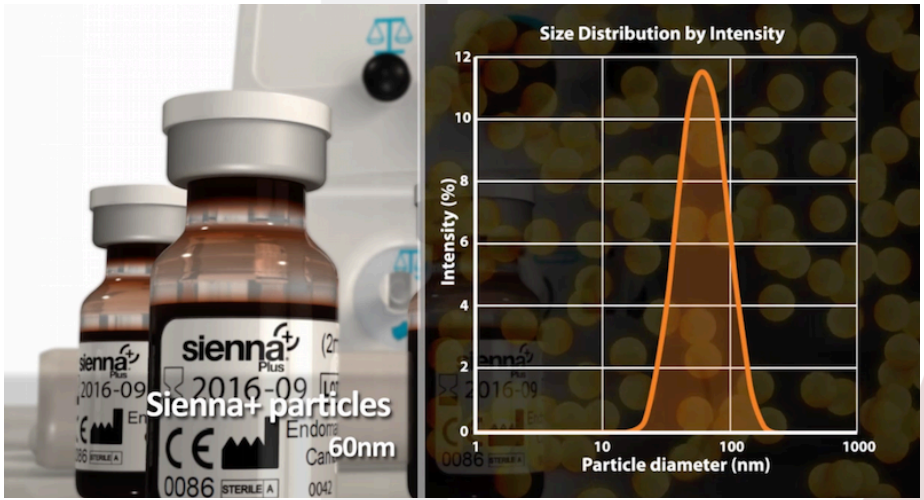




- Dextran-coated iron oxide nanoparticles were retained in the lymph node sinuses
- Particles didn't appear to transit to higher echelon nodes (~100nm diameter)
- But, the rate of transit to the first node was not ideal for impatient surgeons

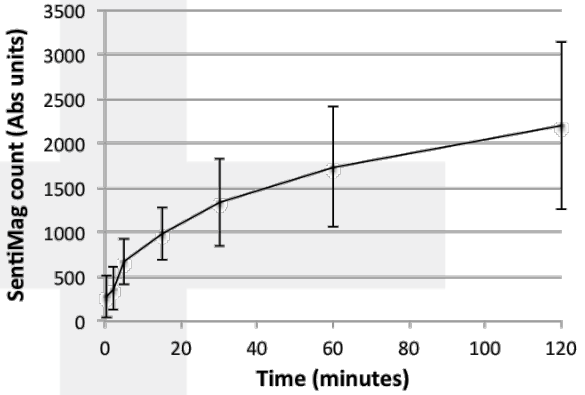
Nanoparticle Selection

- 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

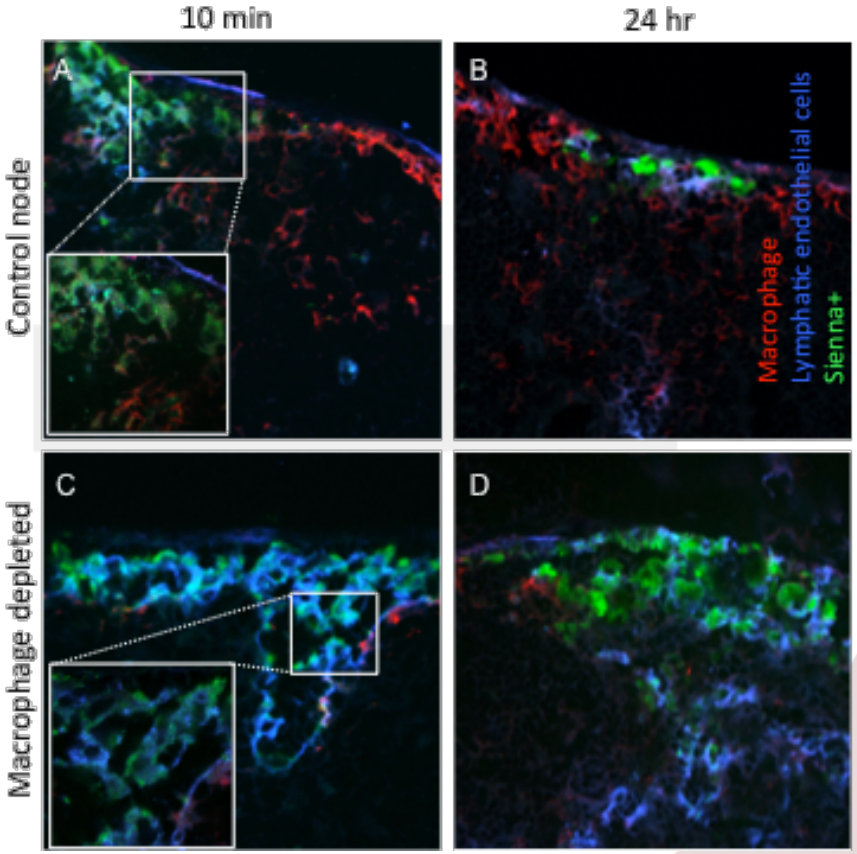
- All MRI contrast enhancement agents are regulated as drugs
- However, Article 1(2)(a) of the Medical Device Directive 93/42/EEC (MDD) suggested that Sienna could be classed as a medical device as it achieves its primary intended action without employing pharmacological, immunological or metabolic means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

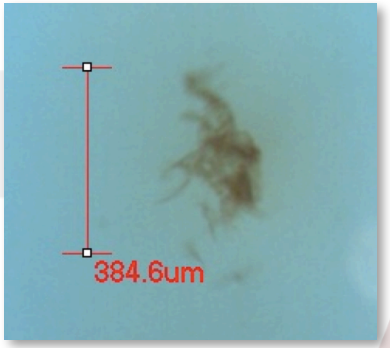


Sienna+ Approval – Europe

- 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

Manufacturing Challenges

- With CE approvals in hand, clinical trials started in Feb 2012
- On Mar 2nd, the Sienna+ packager stated that the 6-month accelerated stability tests had failed visual inspection due to particulates observed by two analysts
- Trial was halted while the nature and root cause of the particulates was investigated
- An independent test house confirmed the particulates were cotton/rayon fibres, and root cause analysis indicated the likely source was the packagers' process
- The particulates were assessed as low-risk as they were infrequent, non-toxic and the sterility of Sienna+ was not compromised
- Notified body accepted inclusion of pre-injection filtration needles



Sienna+ Approval – USA

- In Sep 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 completed in Dec 2015
- PMA review is underway, and Sienna+ is likely to be the first approved nanoparticle medical device in the US later in 2017

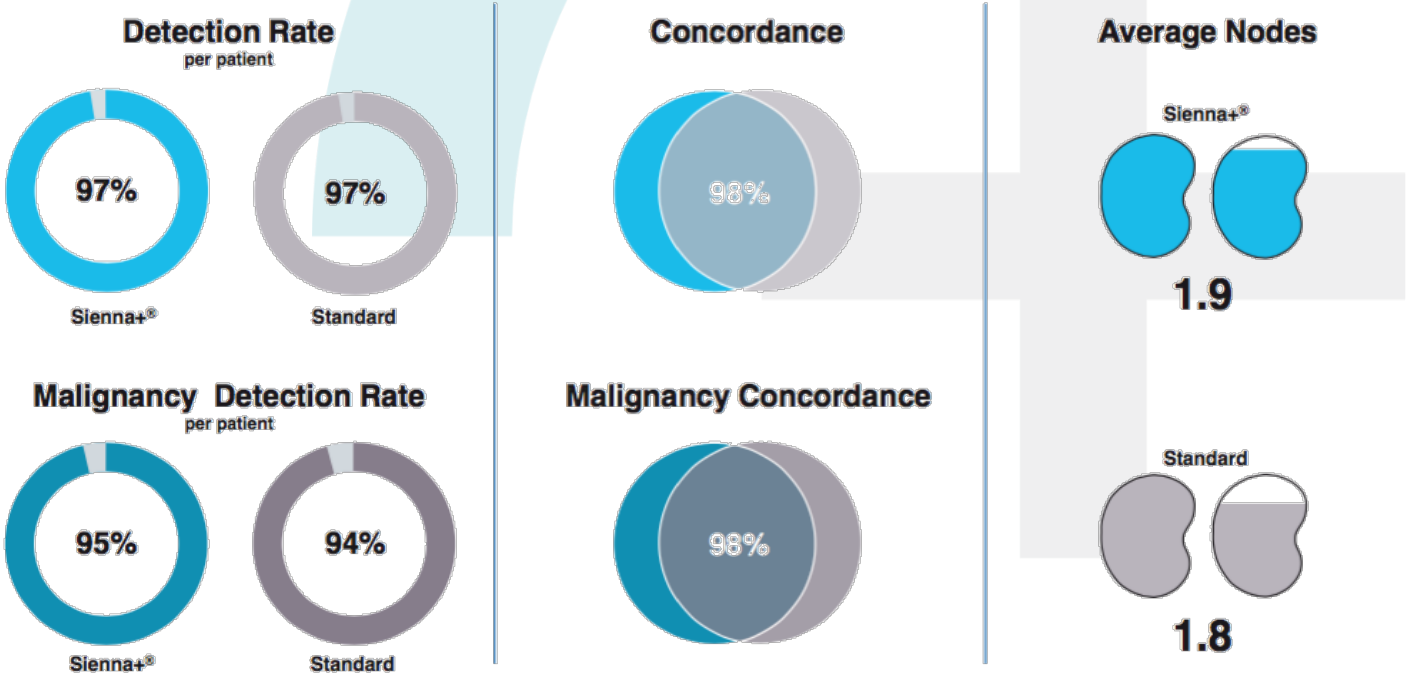
Sienna+®

- Designed for sentinel node localization
- 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 20,000 breast cancer procedures performed
- CE, CMDCAS and ARTG approved
- FDA PMA expected late ’17*

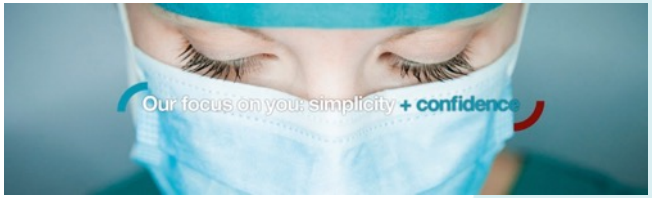
USA: Sienna+/Sentimag are limited to investigational use only under an FDA-approved IDE

Clinical Summary

Results summary including >1,000 breast cancer patients



Epilogue



Leica BIOSYSTEMS North America (Jul 2016)

sysmex EMEA (Feb 2013)

- Headquartered in Cambridge after spinning out from UCL and the University of Houston in 2007
- Revenue-stage with multi-digit growth over last 4 years, following investments totaling £9m
- 2016 sales at £1.6m via strategic distribution partnerships, with 2017 committed at ~£4m
- Treated >20,000 breast cancer patients across 30 countries since launching in Nov 2012
- Expanding international IP portfolio of 15 patent families with 11 patents currently granted

Thank You

Q & A