Due Diligence in Commercialization and Regulatory for Medical Devices

Tales from TECHNA/UHN

TECHNA
ADVANCING TECHNOLOGY FOR HEALTH

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Toronto Research Management Symposium 2016

What is Techna?

An institute of the University Health Network hospital in Toronto, Canada focused on the accelerated development and exploitation of medical technology for improved health.

Measure of Success

A given invention is considered implemented in the clinical setting, if it is properly used for the benefit of the patients, as opposed to being merely operational or installed.

VISION

To be internationally recognized as a leading centre for the productization of medical technology, a hub of a unique, large-scale, clinically-oriented, multidisciplinary, integrated environment.

MISSION

To render medical technologies readily adoptable by the clinical practice and market through provision, facilitation, and coordination of the entire process of medical technology productization.

Techna

How does Techna help adoption of medical technology?

- Agile Design and Derisking:
  - Academic Clinician
  - Technology Development Team
  - Embedded commercialization advice

How is Techna Unique?

- Beyond research – engineering technology to address unmet clinical needs.
- Network of partners – clinicians, academia, industry, and government

Medical Technology

- Hardware
- Software
- Functionalized materials

Developing a Medical Device

- Definition of medical device similar in Canada, US, EU
- Definition of medical device as per Canadian Food and Drugs Act:

  "device" means any article, instrument, apparatus or contrivance, including any component, part or accessory thereof, manufactured, sold or represented for use in

  - **(*a*) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals,**
  - **(*b*) restoring, correcting or modifying a body function or the body structure of human beings or animals,**
  - **(*c*) the diagnosis of pregnancy in human beings or animals, or**
  - **(*d*) the care of human beings or animals during pregnancy and at and after birth of the offspring, including care of the offspring,**

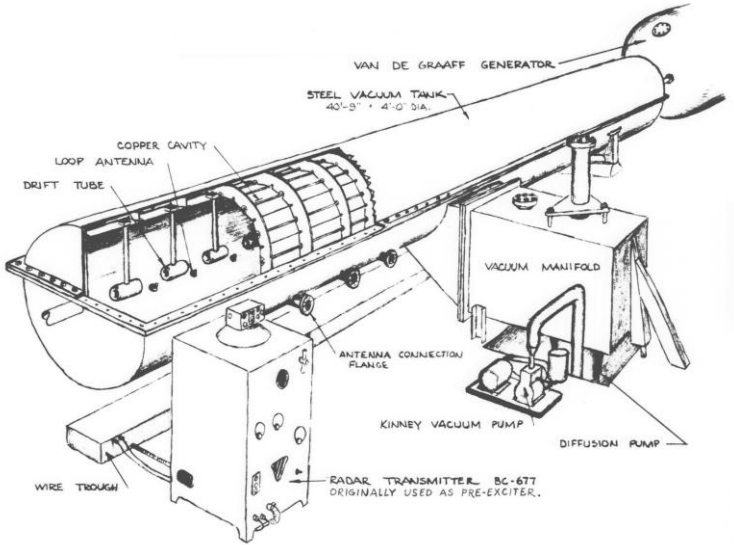
In-House Development...

I have an idea for a medical device that I know everyone will want!

Here's what it is…

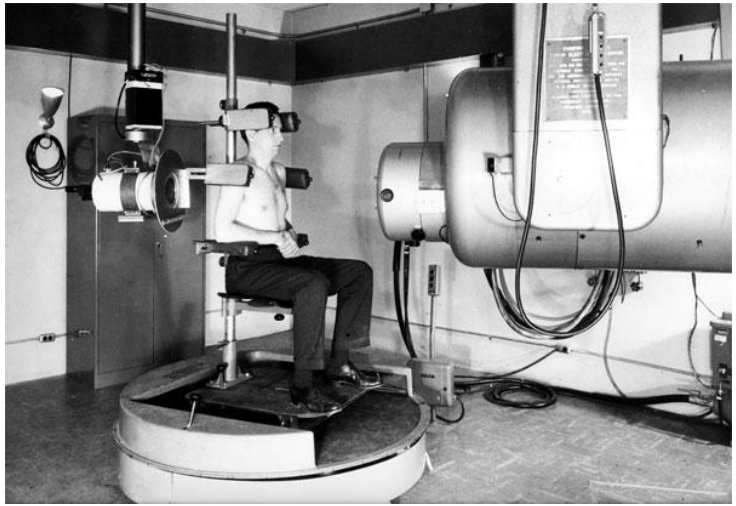
Let me go sketch this out….

AHA! My design is complete…



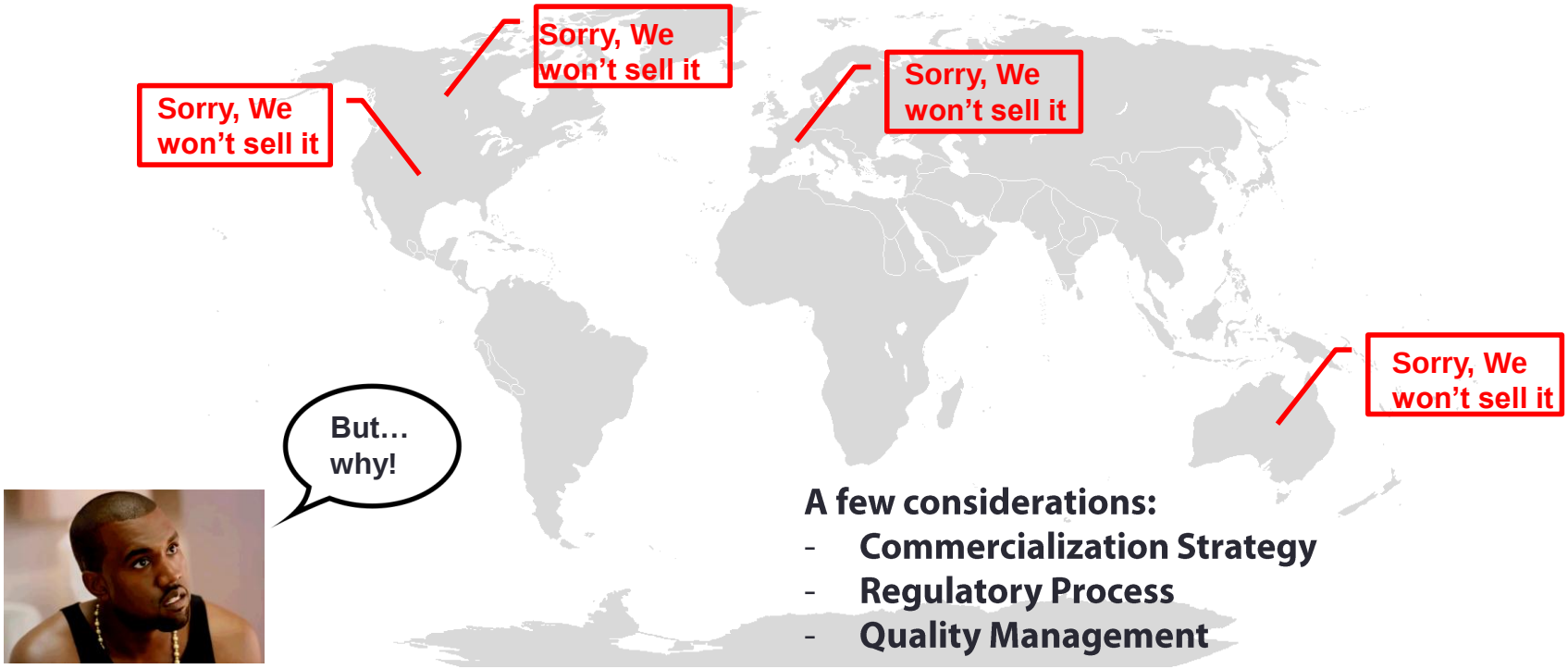
Now time to build…

I've got some excellent grad students who will build this with me



My masterpiece!

Now how to sell it all over the world?



A few considerations:

- **Commercialization Strategy**
- **Regulatory Process**
- **Quality Management**

Commercial Relationships

Traditional University-type license
- "Fire and forget", very early stage, little validation

NONE

Traditional 'NERF' Sponsored Research
- Never results in successful commercial relationship

'Commercial' Sponsored Research
- Results in successful commercial relationship

License and Co-Development
- Tech. developed and early validation at UHN
- Frequently solves a hospital problem, implements clinically
- Industry prod. dev., UHN co-dev., testing and/or validation

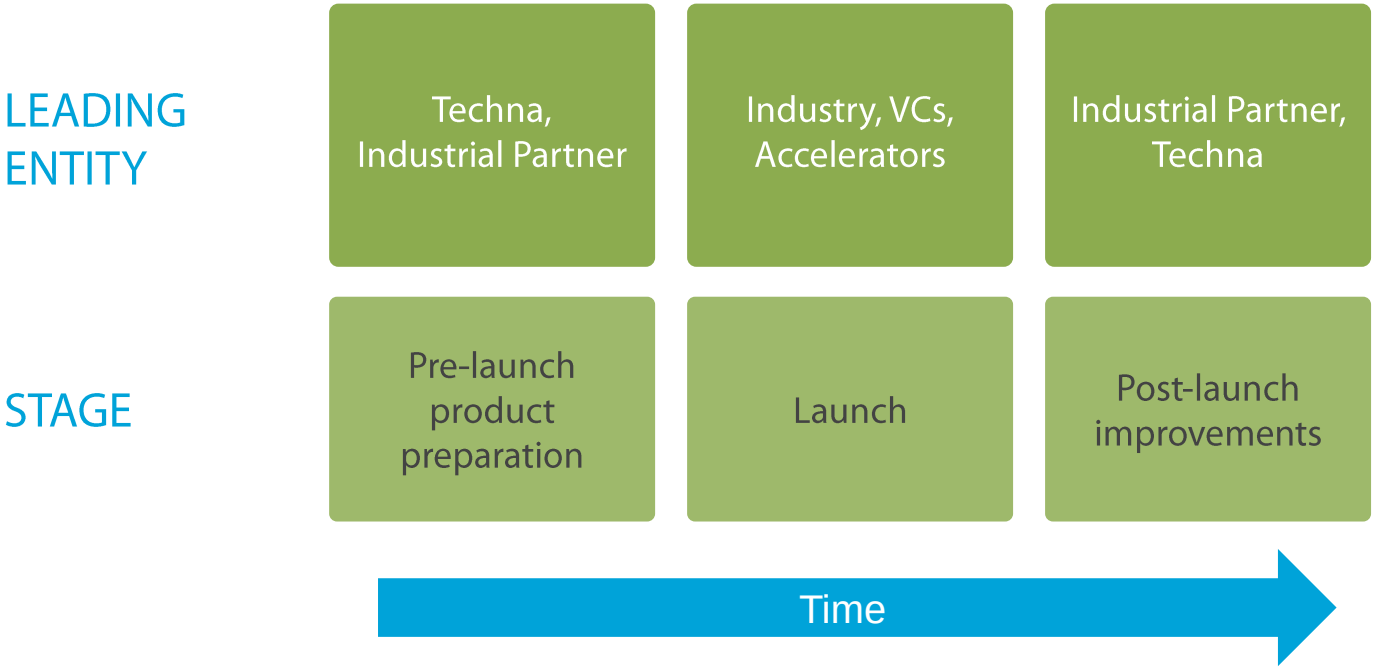
License and Product Co-Development
- Our most successful relationships
- UHN responsible for prod. dev., test, validation, product support
- Mostly s/w, i.e. UHN created go-to-market source-code product

Product Specification
- Industry (pro-dev.) plus UHN (know-how, testing, validation, clinical implementation)

Majority-Owned Start Up

TECHNA

Commercialization



Co-dev Considerations

Before embarking on an initiative that will involve a collaboration with a third party (e.g. public, private, mixed), specifically using a co-design/co-development approach, there are a number of considerations to review:

- **Funding Source** – Identifying the financial source determines which policies and regulations will apply to the project: who is paying for the work done (UHN operations, grant, one of the foundations, industrial partner, the government).

- **Procurement** – Purchasing of goods and services using public funds has to be aligned to the Broader Public Sector Directives. Partners and funders may have additional regulations. In case of co-development which requires purchasing from the collaborator, there is often a valid case for sole sourcing from the collaborator.

- **Conflict of Interest** – UHN employees involved in the project have to disclose any potential Conflict of Interest.

- **Non-Disclosure Agreement (NDA)** – NDAs have to be executed between all parties prior to disclosing any confidential information related to the project, product, process, or strategy.

- **Signing Authority and Delegation (SADP)** – Depending on the type and value of the purchase or the project, different sign offs are required from the UHN personnel and executives. UHN's SADP should be revised prior to the project initiation to determine whether the approvals are likely to be solicited.

Co-dev Considerations

- **Research Ethics Board (REB)** – Work that involves human subjects may require REB approval.
- **Commercialization/Licensing** – Commercialization strategy needs to be agreed upon between all the parties, especially the desired and expected ownership of the Intellectual Property.
- **Accountability for Future Operations** – If the result of the project needs to be sustained operationally beyond the development, the party responsible for providing the operational support needs to be determined.
- **Governance** – Program/project governance should be agreed upon by all the participating parties and corresponding teams, including how accountabilities and escalations will be managed.
- **Resource/Financial Model** – The funds available for the project have to be evaluated against the expected work to be carried out.
- **Legal/Contracts** – In case of co-development, one or more of the UHN Departments may be involved or lead the contractual agreements: general counsel, Technology Development and Commercialization (TDC) Office, Grants and Contracts, external legal counsel. The leading entity should be determined

.

- **Personal Health Information** – During co-development care must be taken to protect the privacy of patients and security of the data. Expectations related to access and ownership of any PHI have to be clarified and agreed upon.

Quality and Regulatory

Why is there a need for regulations in medical devices in the first place?

- Safety → Risk
- Intended Use → Effectiveness
- Quality

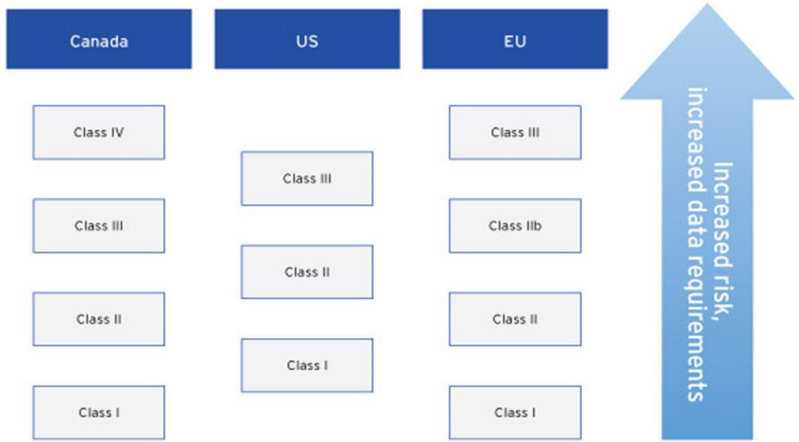
Regulatory

Three main markets for medical devices:

Health Canada

FDA

CE



Regulatory

- Global Harmonization Task Force (1992-2012)
  - Aiming to harmonize regulations worldwide
  - Five founding members: US, Canada, Japan, Australia and EU
  - Five study groups:
    - Propose and finalize guidance documents for pre-market regulatory, labeling, post-marketing surveillance, clinical safety, quality system, and auditing requirements
- In 2012, GHTF was dissolved and International Medical Devices Regulators Forum (IMDRF) was formed on the foundational work done by GHTF

Regulatory

- International Medical Devices Regulators Forum (IMDRF):
  - IMDRF Management Committee
    - The current members are: Australia, Brazil, Canada, Europe, Japan, and the United States of America.
    - The World Health Organization (WHO) is an official observer.
- Work by GHTF/IMDRF is being adopted by countries with emerging regulatory regimes

IMDRF International Medical Device Regulators Forum

Quality

- ISO 13485 is a standards document created by the "**International Organization for Standardization**"
- A comprehensive quality management system for the design and manufacture of medical devices
- Tailored to industry's expectations in quality management and regulatory requirements
- Aids in achieving a vast majority of the requirements f Health Canada, FDA and Europe

Main Aspects of ISO 13485

1. **Section 4 - Quality Management System** – Document control, Records control etc.
2. **Section 5 - Management Responsibility** – Customer focus, Management review etc.
3. **Section 6 - Resource Management** – Work environment (ISO 27799, Human resource, Training etc.
4. **Section 7 - Product Realization** – Design and development (IEC 62304, 60601, etc), Purchasing, Support etc.
5. **Section 8 - Measurement/Analysis/Improvement** – Control of non-conforming product, Analysis of data etc.

Integral Quality Monitor – IQM

- Invented at the Princess Margaret for real-time monitoring of radiotherapy beam
- Commercialization Type:

  2012 - License and Product Co-Development (+ Royalties)
- Co-Developed inside the hospital in a partnership with a commercial partner (iRT GmbH), an international start-up
- Leveraged clinical and commercial knowledge
- 20+ Beta sites deployed globally, clinical deployment started
- ISO 13485 Certified, CE Certified, Health Canada Certified (Class III), FDA Certified (Class II).

* Presented at the Health Research Caucus on Parliament Hill, Oct 2014

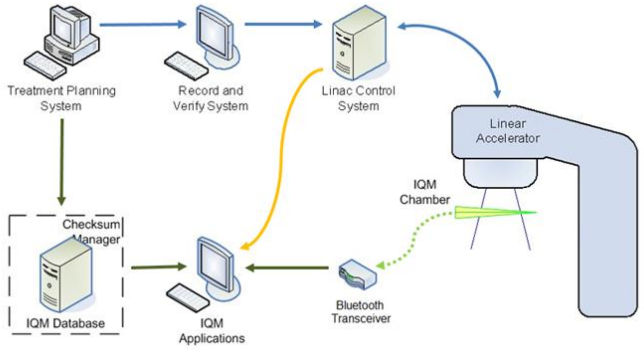
Integral Quality Monitor – IQM

KEY TECHNA/UHN ACTIVITIES

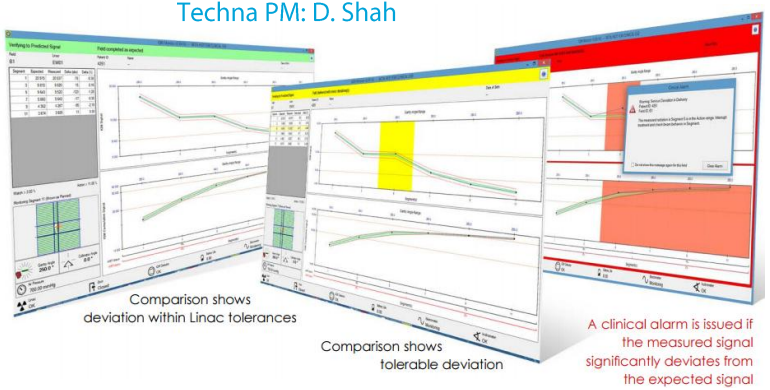
Software: Development, Verification, Validation, Service/Support and Maintenance

Hardware: Validation of new prototypes, Service/Support and Maintenance

QMS – Adherence to procedures outlined by industry partner (iRT)



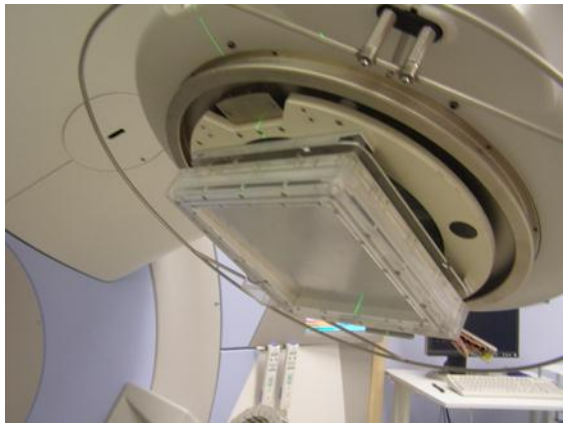
PIs: M. Islam, R. Heaton, D. Jaffray
Techna PM: D. Shah

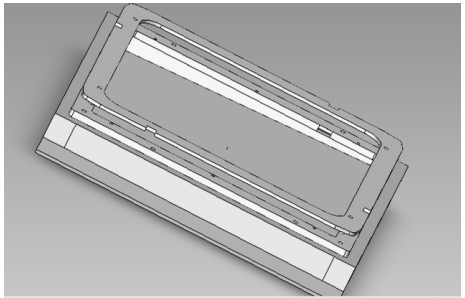


Integral Quality Monitor – IQM

LESSONS LEARNED

1. Lengthy co-development period (2012 - 2016+)
2. Funding sources – limited due to international start up
3. High level of testing – FDA, CE, Health Canada
4. Building a QMS which encompasses UHN activities
5. Minimal defined requirements (prototype) = Limited risk assessment
6. Separating Research from Co-Development/Product

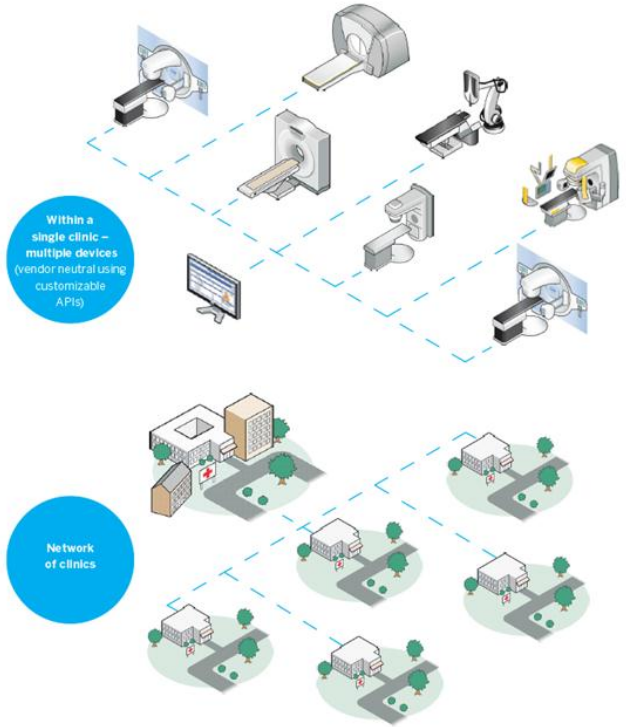




AQUA

- Invented at Princess Margaret to address efficiency and integrity
- A quality management software for the quality control and management (QC&M) of radiation oncology treatment and imaging equipment
- Provides automated and comprehensive quality assurance for LINACs
- Scalable from single location to distributed network of clinics/hospitals
- To-do list and dashboard for compliance and performance
- Reduces cost of QC with test automation
- Commercialization Type:

2014 - UHN Majority Owned Start-Up



acumyn
CONFIDENCE IN CARE

PIs: D. Latourneau, D. Jaffray
PM: D. Shah

AQUA

KEY UHN/TECHNA ACTIVITIES

Software: Design and Development

Quality: Implementation and oversight of ISO 13485:2003, ISO 9001:2008, IEC 62304, Ongoing implementation of ISO 27002/27799 (Information Security Management in Health)

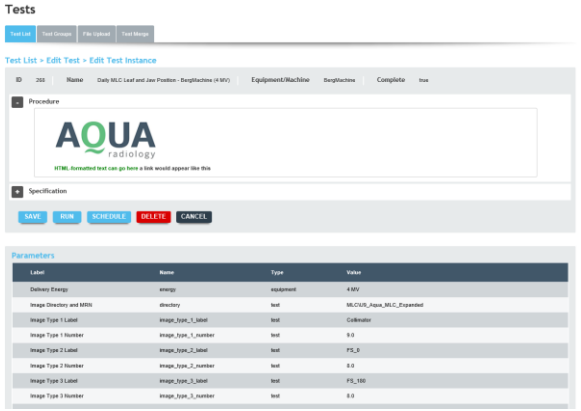
Writing: Technical and Grant Writing

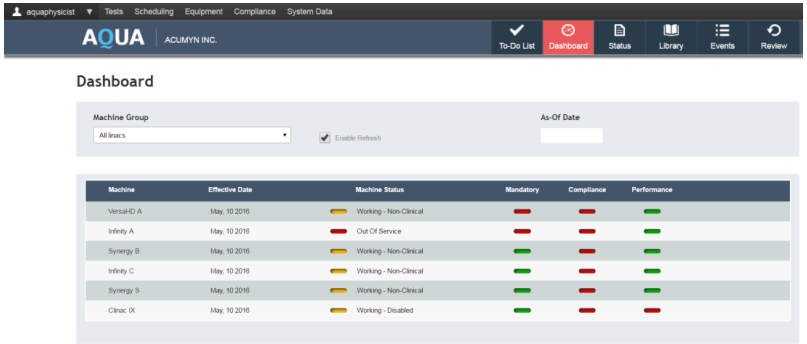
Marketing: Website development, conference brochures,

videos

Financial: Accounting support

Contracts: Complex deal negotiations involving large multinationals

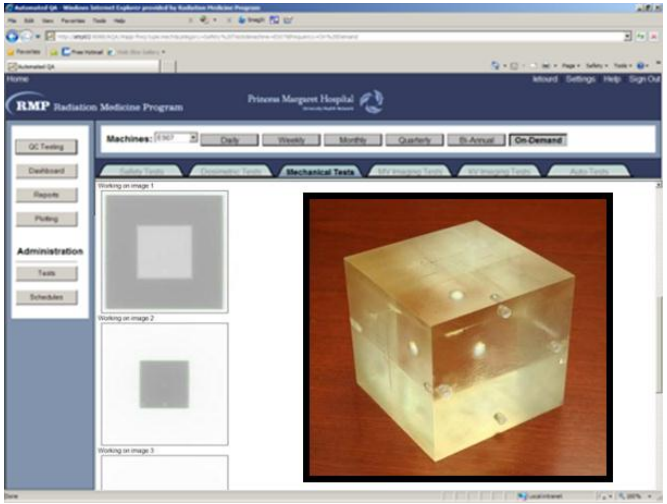




AQUA

LESSONS LEARNED

1. Building a QMS from scratch
2. Working with large international partner – Elekta: Who's the driver? Who sets the tone?
3. Building a strong team
4. Access to UHN facilities to validate
5. Building a baseline product requirements = Limited risk assessment



Common Themes

- Devices built as a research tool can easily be introduced into the clinical setting due to the ITA loophole
- In many cases, a thorough risk assessment following guidelines such as ISO 14971 - Medical devices -- Application of risk management to medical devices, is not performed
- Separating ongoing research from a commercially viable product
- High turnover of research staff makes concepts like change control challenging
- Easier to work with and find industry partner if there is some quality management during development

THANK YOU

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Legal Implications

- **Medical Devices Regulations (SOR/98–282)**. Schedule 1. Classification rules for medical devices.
- Part 1 – Medical devices other than *in vitro* diagnostic devices
- Part 2 – *In vitro* diagnostic devices
- Cost: ~$7500 - $22,000

Classification

Medical device classification system			
Device Class	Risk	Examples	Licence Requirements
Class I	Lowest	Surgical instruments, laboratory culture media	A device licence is not required, but the establishment where it is made and/or distributed must be licensed.
Class II	Low	Contact lenses, pregnancy test kits, endoscopes, ultrasound scanners	Manufacturers require a Health Canada licence before selling or advertising Class II, III and IV devices. Annual licence renewals are required.
Class III	Moderate	Orthopedic implants, glucose monitors, dental implants, hemodialysis machines	
Class IV	High	Cardiac pacemakers, angiography catheters, cranial shunts	

Table 1: Health Canada medical Device Classification System

Legal Implications

- Code of Federal Regula  62–892
- Cost: ~$4000 - $270,000

Classification

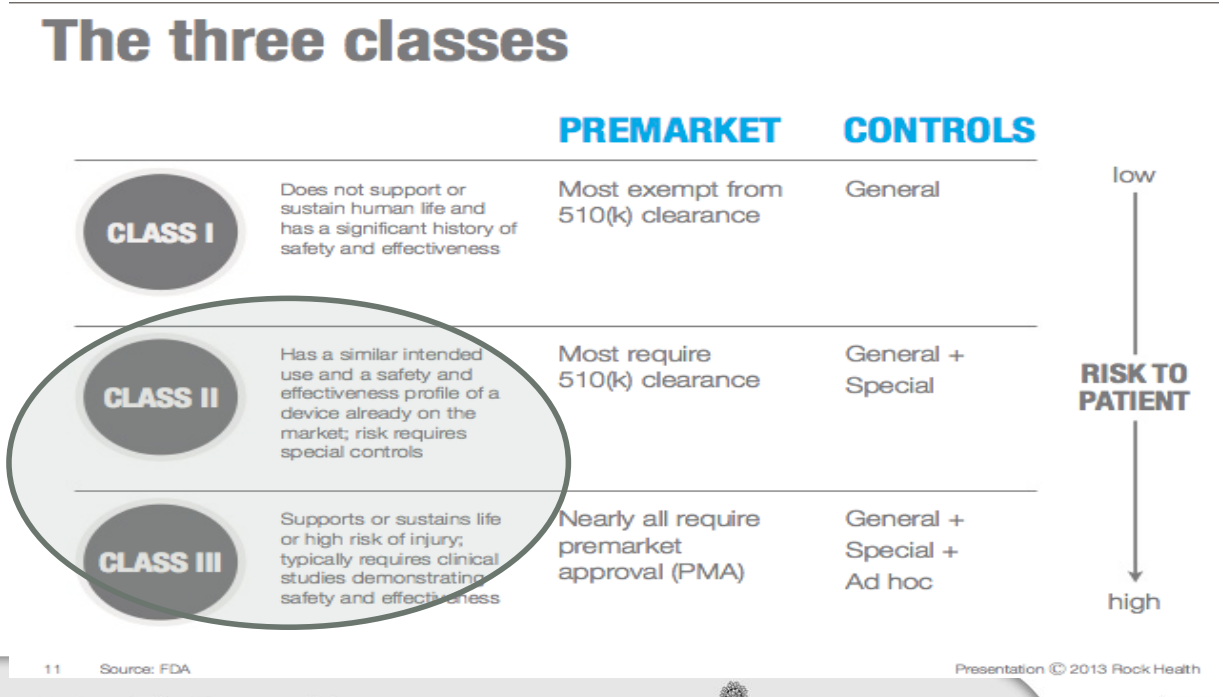
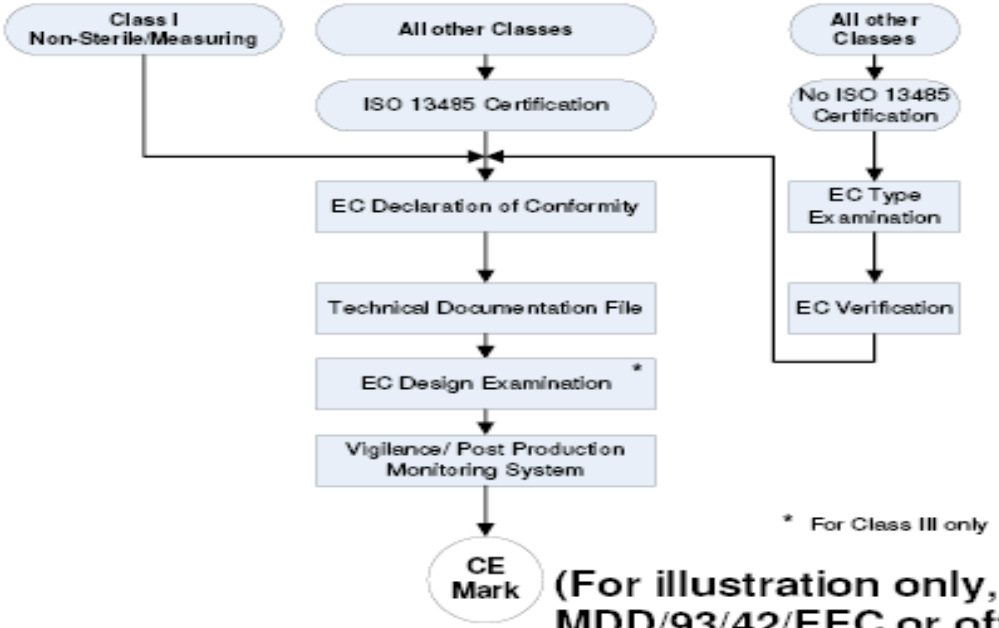


Table 2: FDA Medical Device Classification System

Legal Implications

- **Medical Device Directive 93/42/EEC** regulates most devices. Classification rules are listed in Annex IX of the directive.
- **Active Implantable Medical Devices (AIMDs) Directive 90/385/EEC**. AIMDs are regulated as high-risk devices.
- ***In Vitro* Diagnostics (IVDs) Directive 98/79/EC**. Most IVDs are regulated as low-risk devices, except for tests that underpin the safety of blood and blood products (blood group, HIV and hepatitis tests), where additional specific requirements equating to a high-risk category apply.
- **Subsequent directives:** A number of additional directives amending the original directives have been introduced:
- Directive 2007/47/EC amends Directive 90/385/EEC and Directive 93/42/EEC
- Directive 2001/104/EC brings medical devices incorporating stable blood derivatives within the scope of the general directive
- Directive 2003/12/EC reclassifies breast implants into class III
- Directive 2003/32/EC relates to medical devices that are manufactured utilizing tissues of animal origin
- Directive 2005/50/EC reclassifies total hip, knee and shoulder joints into class III

Legal Implications



(For illustration only, please see MDD/93/42/EEC or official routes.)

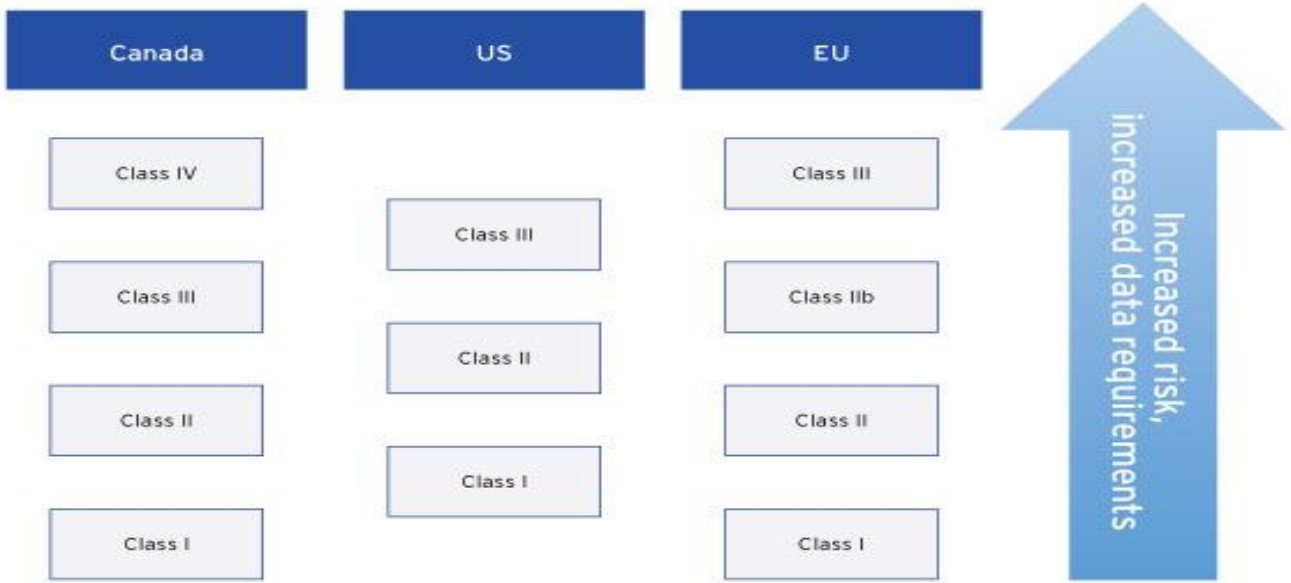
Classification

Class	Requirements	Examples
I	All non-invasive devices*	Non-sterile dressings used to aid the healing of a sprain, plaster of Paris, cervical collars, gravity traction devices, compression hosiery, stethoscopes, electrodes for EEG or ECG
IIa	Surgically invasive devices intended for transient or short term use*	Surgical swabs, syringe needles, staplers, surgical gloves, dental aspirator tips, clamps, temporary filling materials, bridges and crowns, dental alloys
IIb	All implantable devices and long-term surgically invasive devices *	Intra-ocular lenses, insulin pens, dialysis equipment, ventilators
III	All devices incorporating, as an integral part, a substance which is liable to act on the human body with action ancillary to that of the devices or anything in direct contact with the heart*	Antibiotic bone cements , condoms with spermicide, heparin coated catheters, endodontic materials with antibiotics, prosthetic heart valves, aneurysm clips, vascular stents, IUD

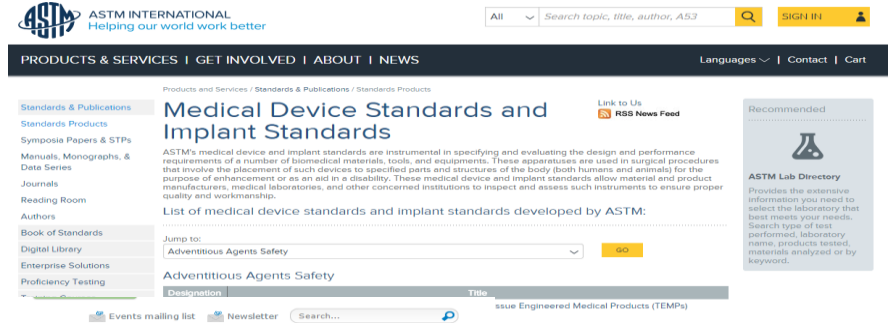
Table 3: EU Medical Device Classification System

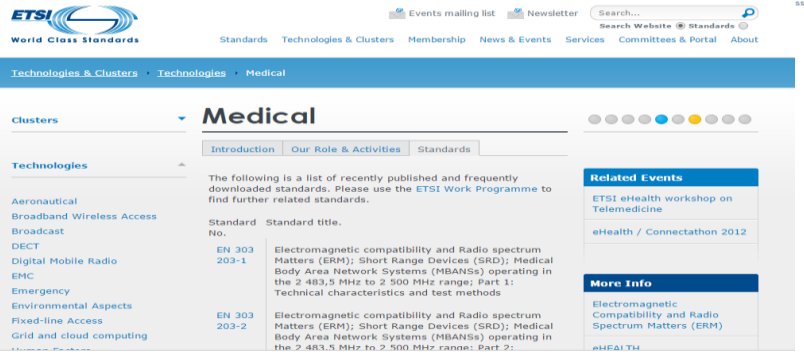
http://ec.europa.eu/health/medical-devices/files/meddev/2_4_1_rev_9_classification_en.pdf

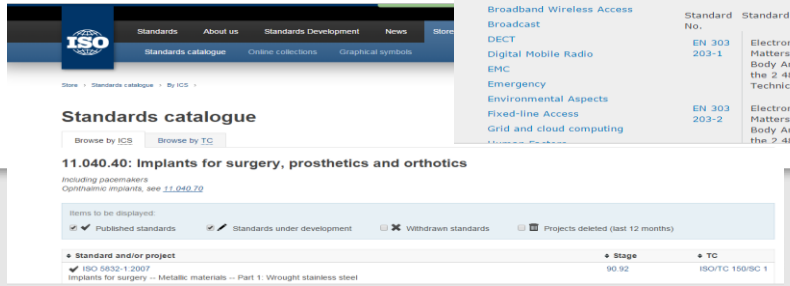
Classification

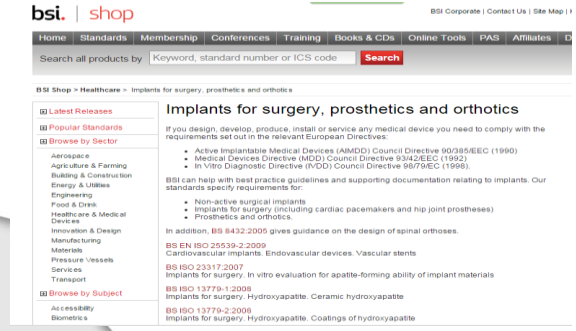


And there's more!









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Premarket Regulatory Requirements for US: Establishment Registration

- Medical devices regulated by FDA
- Establishment Registration
  - Compliance with Quality Systems Regulations (QSR) 21 CFR 820
  - Requirements pertaining to designing, purchasing, manufacturing, packaging, labeling, storing, installing and servicing of medical devices
  - Design controls: Compliance during design and development of the device
  - Manufacturing facility subject to FDA Inspections

Quality System Requirement: US

Product Registration: US

- Classification of medical device:
  - Product Code Classification Database
  - Classification Regulations 21 CFR 868-892
- Class I: least risky -→ General Controls.
- Class II: Additional S & E requirements → General and Special Controls
- Class III: Most risky, support or sustain human life, Most stringent regulatory requirements → General Controls and Premarket Approval

Product Registration: US

Classification	General Controls (Establishment Registration, Med Dev Listing, Labeling Req., QSR)	Special Controls (Special labeling requirements, Mandatory performance standards, Post-market surveillance)	Premarket Notification (510k)/Approval (PMA)
1	Required	Not Required	Usually exempt from 510(k) requirements
2		Required	510(k) required
3		Required	PMA Required

510(k) and PMA: US

	510(k)	PMA
Type of device	Class II and some class III	High risk Class III devices
Key requirement	Predicate device required for establishing substantial equivalence (SE)	Clinical Studies required
Submission req.	SE comparison with predicate, device performance test results, verification & validation results)	Detailed scientific review of device information, test results, more detailed information
Clinical studies	Depending on the similarities and differences with predicate device, may/may not require clinical studies	Always require clinical studies

510(k) and PMA: US

	510(k)	PMA
Quality System Evaluation	Subject to FDA inspections but not required prior to clearance	FDA inspection required before approval
Fees	Std.: $5170; SB: $2585	Std.: $258,520; SB: $64,630
Time to review	~3-4 months	~at least 1 year
Additional Req	N/A	May require post approval post marketing commitments like sending safety and effectiveness reports and Post Marketing Surveillance Studies

Premarket Regulatory Requirements: EU

- Medical Device Directive 93/42/EEC (MDD)
- May require compliance with other directives like Active Implantable Medical Directive, In Vitro Diagnostic Directive, depending on type of the medical device
- Involvement of Notified Body
  - ISO 13485 registration by Notified Body

Establishment Registration: EU

- Establishment Registration:
  - ISO 13485 registration by Notified Body
    - Requires compliance to ISO 13485:2003 and EU MDD requirements
    - 77 Notified Bodies (NB)

Product Registration: EU

- Depending on the classification of the device, requires involvement of NB
- More risky device → More involvement of NB
- Classification of device: 18 Classification rules in Annex IX of MDD: Class I (non-sterile, sterile, measuring, non-measuring), Class IIa, IIb, and III

Premarket Regulatory Requirements: EU

- EU Conformity Assessment Routes:
  - Determined in conjunction with the NB
  - Most popular: Full Quality System (ISO 13485), Review of Technical File by NB, CE mark

Product Registration: EU

Classification	Involvement of NB	Involvement of EUAR	Technical File Requirement	CE Mark
I (non-sterile and non-measuring)	Minimal	Required	Required for files; but self-declaration); TF: Device info, risk analysis, Essential Requirements, Testing data, Design and change control, clinical evaluation	CE without a number
I (sterile and measuring)	Required		Required and to be reviewed by NB; TF: Same as for Class I non-sterile, non-measuring + sterilization and/or measuring validation data	CE with a NB number
IIa	Required		Required and to be reviewed by NB TF: Same as for Class I non-sterile, n on-measuring + sterilization and/or measuring validation data, clinical evaluation	
IIb	Required			
III	Required		Required and to be reviewed by NB: Same as above +device design, More extensive testing data and clinical evaluation	

Premarket Regulatory Requirements: EU

- EU Authorized Representative
- Registration of the medical devices in the various EU member states
- Post Marketing Surveillance Activities:
  - Vigilance Reporting
  - Recalls
  - Feedback
- Labeling requirements:
  - In accordance with Annex 1 of MDD
  - Language requirements for labeling
  - Labeling translation in EU languages

Recent Changes: EU

- Changes in EU regulations
  - Emerging from historical regulatory issues with PIP scandal
  - Consideration of more oversight over Notified Bodies
  - Unannounced inspections/audits by Notified Bodies
  - More stringent reviews of higher class devices