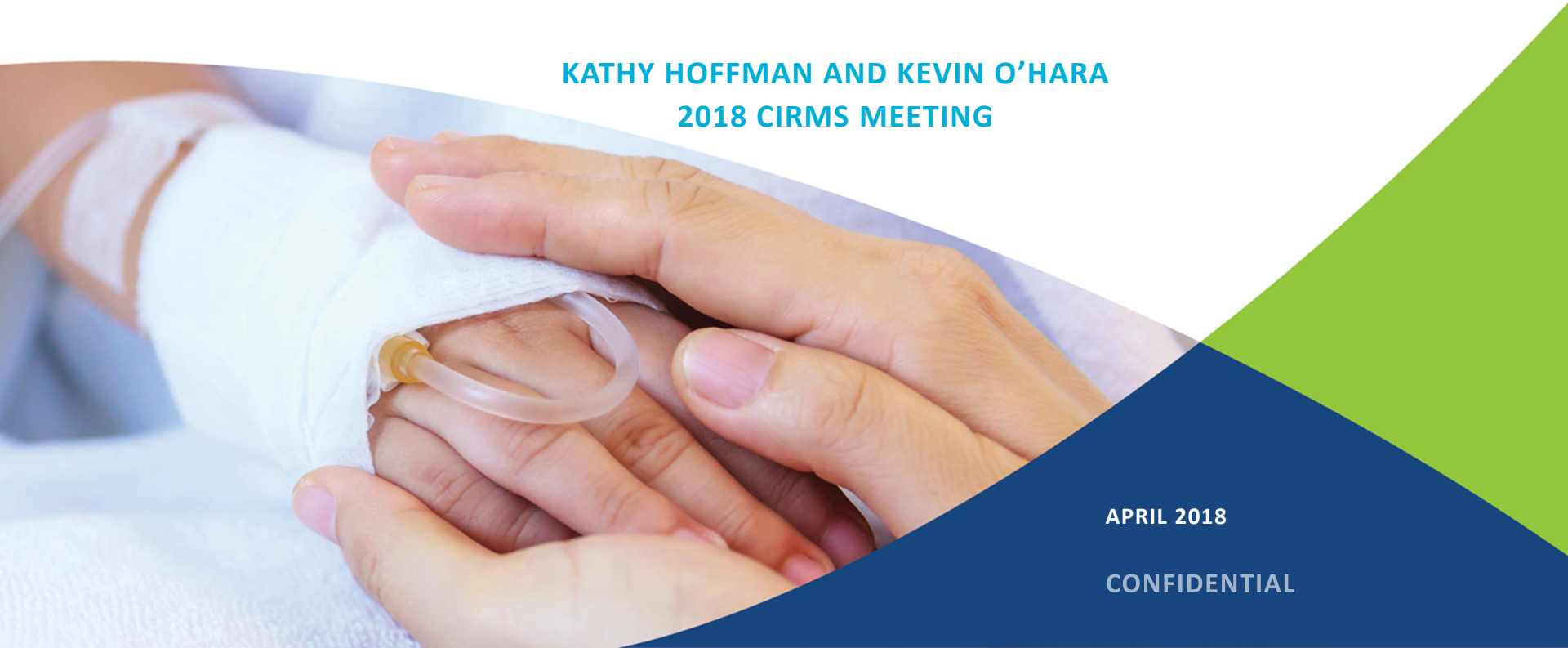


The Future of Radiation Sterilization - The Perspective of a Contract Service Provider

KATHY HOFFMAN AND KEVIN O'HARA
2018 CIRMS MEETING



APRIL 2018

CONFIDENTIAL

Scope

- A brief overview of the healthcare industry today, and the pace of technology advancement.
- Increasing complexities of the radiation-processing world due to technology advancement.
 - The need for the radiation-processing industry to find ways to minimize radiation damage, develop new approaches, partner with the device manufacturer in an increasingly complicated regulatory environment.
- iiA 2017 Publication
 - A Comparison of Gamma, E-beam, X-ray and Ethylene Oxide Technologies for the Sterilization of Medical Devices and other Products.
- Discussion

New Publication

- A Comparison of Gamma, E-beam, X-ray and Ethylene Oxide Technologies for the Sterilization of Medical Devices and other Products
 - Published by the iia in 2017
 - www.iiaaglobal.com
 - Brief overview in today's presentation



white paper

A Comparison of Gamma,
E-beam, X-ray and
Ethylene Oxide Technologies
for the Industrial Sterilization
of Medical Devices and
Healthcare Products

AUGUST 31, 2017

Safeguarding Global Health™



Expert Lab Testing and Consulting

Safeguarding Global Health – with every test we complete.



Gamma Technologies (GT)

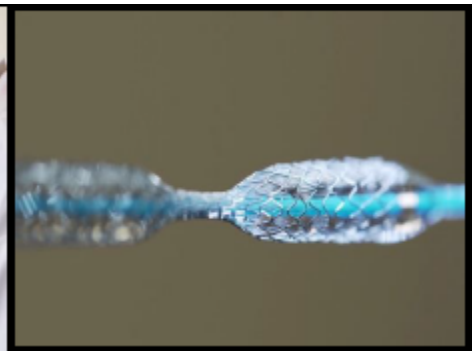
Medical Isotopes (MI)

Safeguarding Global Health – with every critical isotope we supply.



Comprehensive Sterilization Services

Safeguarding Global Health – with every product we sterilize.



- Pre-FDA Validation & Quality Control testing of the stent, pacemaker, vaccine & syringe, protective gowns/masks, and all IV tubes
- Creates the cleaning protocols for medical equipment used in operating room procedures



- Radioisotopes used for diagnostic imaging, Gamma rays for Gamma Knife treatment used on brain tumors



- Conducts the sterilization process & post sterilization validation of the stent, pacemaker, drapes, gowns, masks, tubing, syringe & vaccine and bandages

Keeping up with the Device Manufacturer

The convergence of technologies has and will continue to drive the development of ever-more complex sterile health care products

Treatment of symptoms → Cure

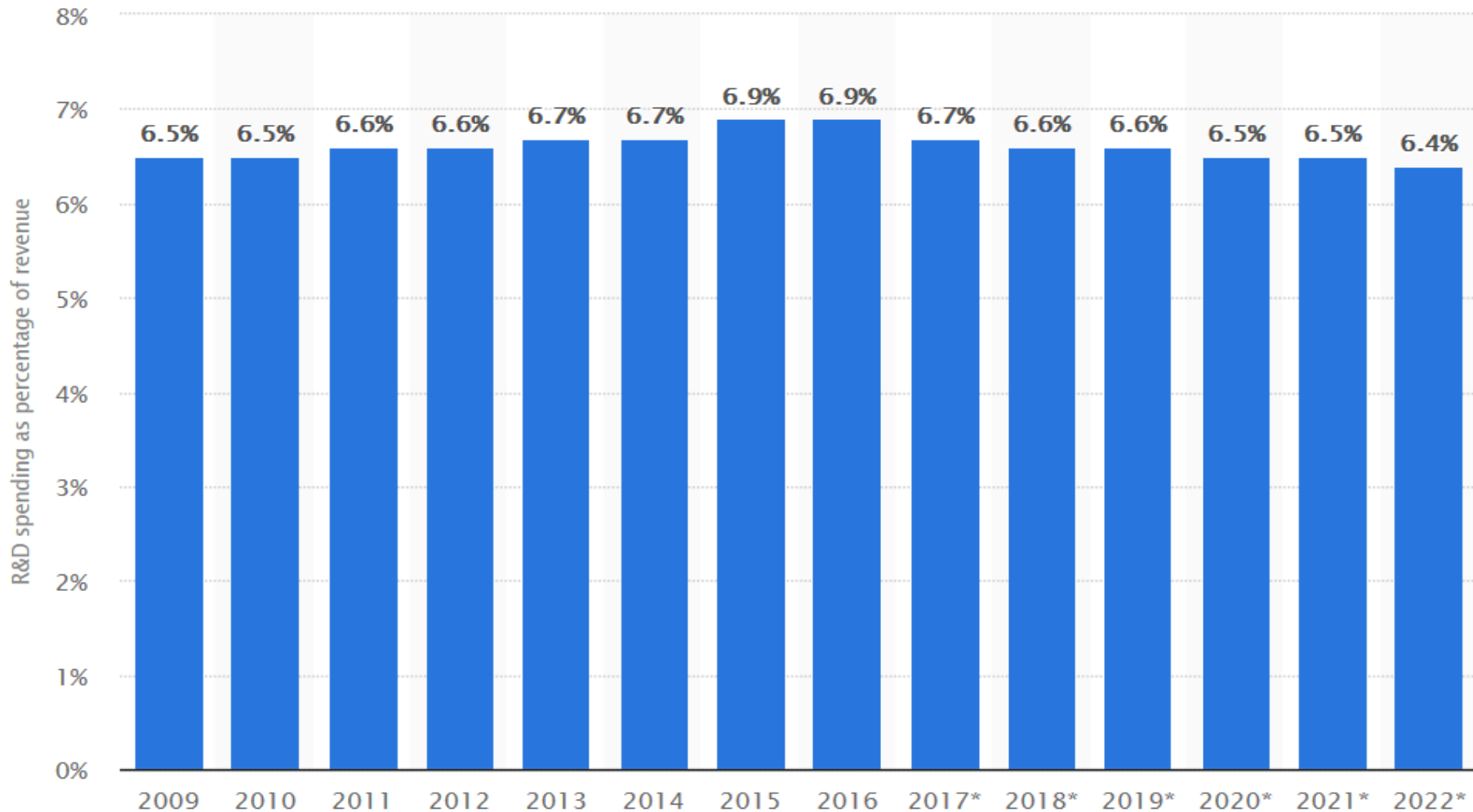
But, with much more emphasis on prevention

To succeed in this environment the radiation processing industry must

- Discover techniques to minimize radiation damage to bioactives and fragile molecules
- Develop specialized equipment
- Partner with a diverse group of health care product developers
- Function in a more complex regulatory environment

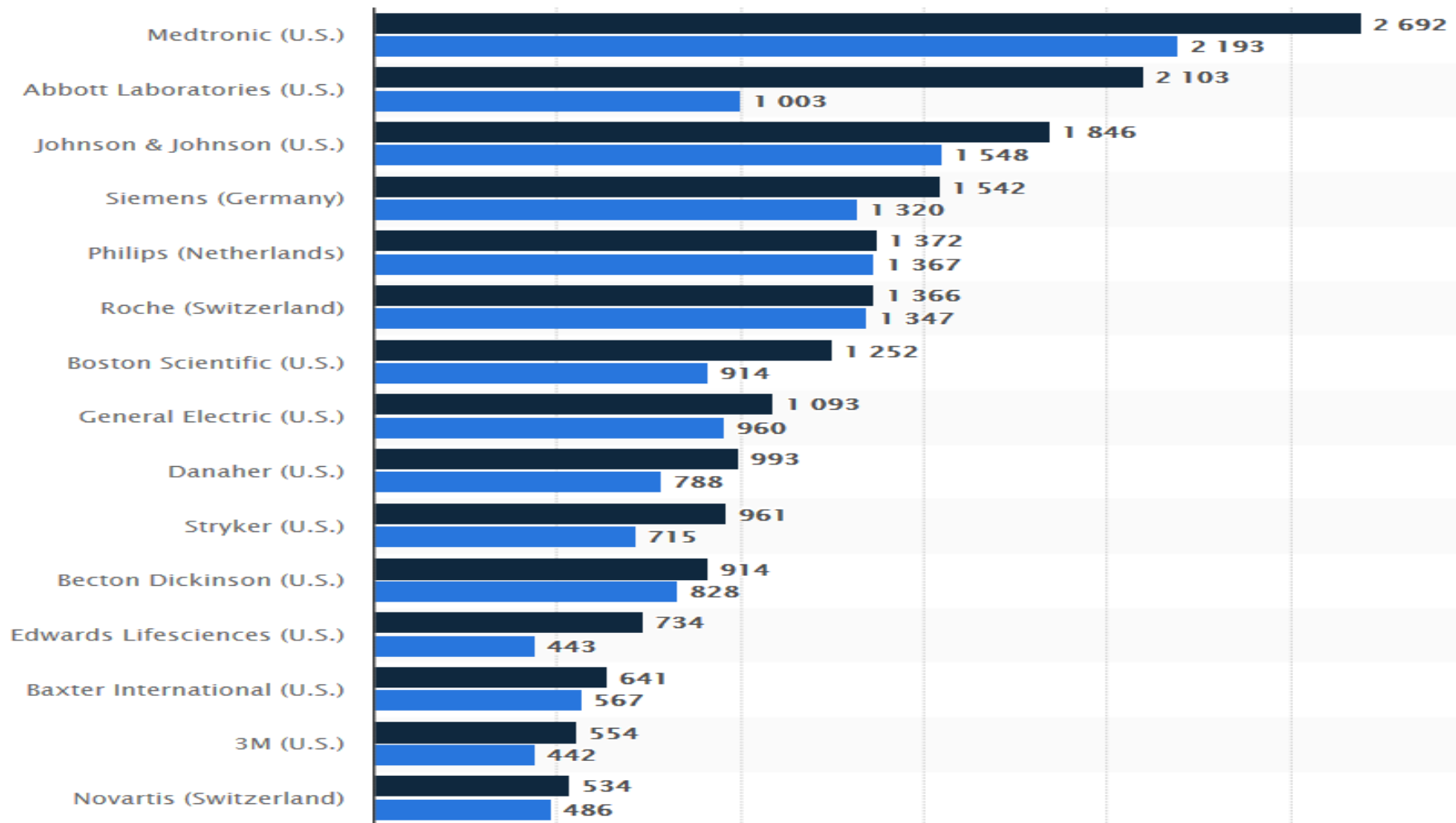
(Liu, 2007)

Worldwide Medical Technology R&D Spending



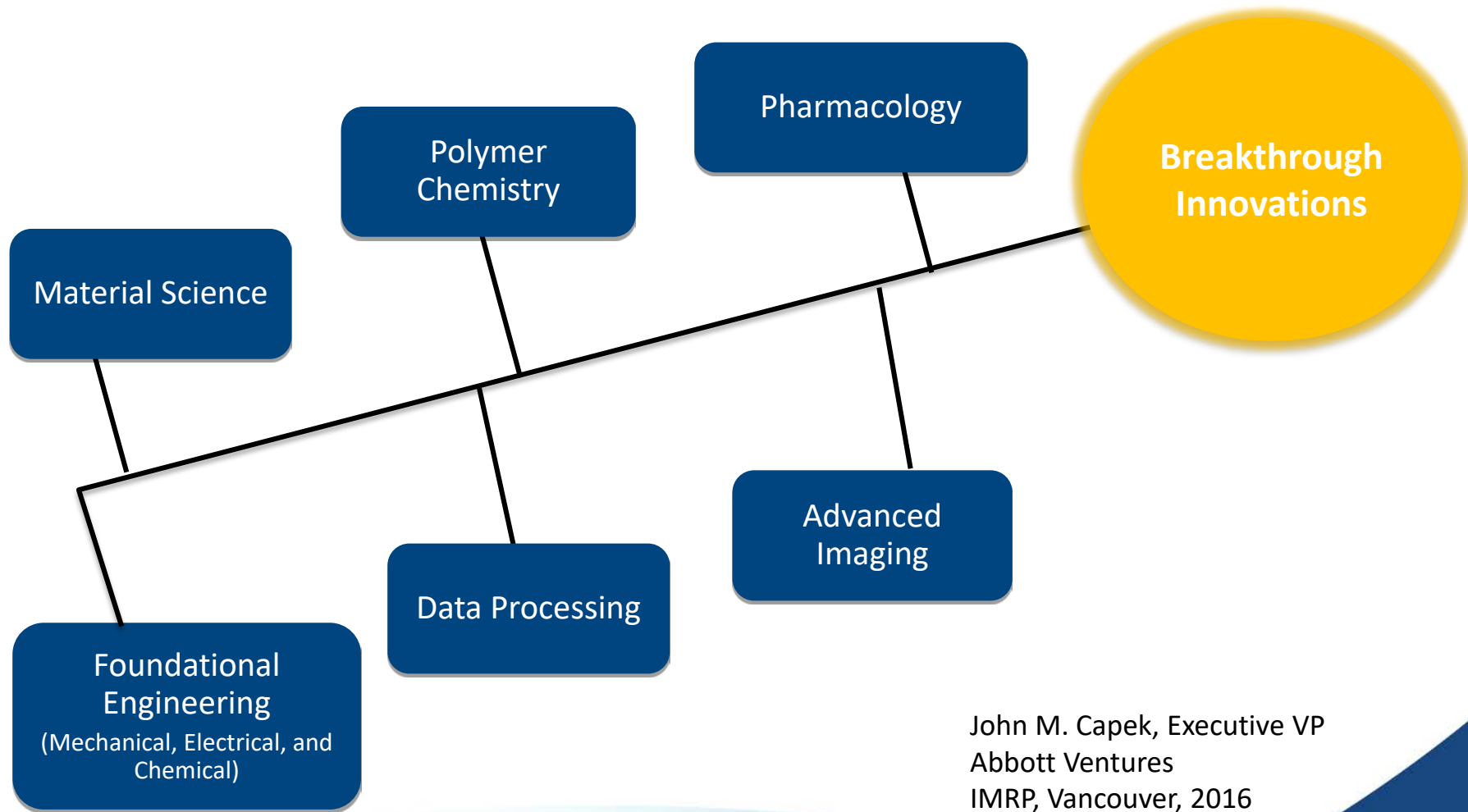
R&D Spending as a Percentage of Sales Revenue. Source: Statistica.com 2018

Med. Technology R&D Spending by Company



R&D Spending in 2015; projected for 2022. Source: Statistica.com 2018

Advancements in Science and Technology Have Made Innovations Possible



Complexity of Medical Device Evaluations

Cytotoxicity

- assess interaction of medical device or extract with mammalian cells.

Sensitization

- estimate the potential for contact sensitization by medical device or extract.

Irritation

- measures the irritation potential of the medical device or extract.

Systemic Toxicity

- assesses the toxicity potential of the leachables and degradation products upon single or multiple exposures.

Genotoxicity

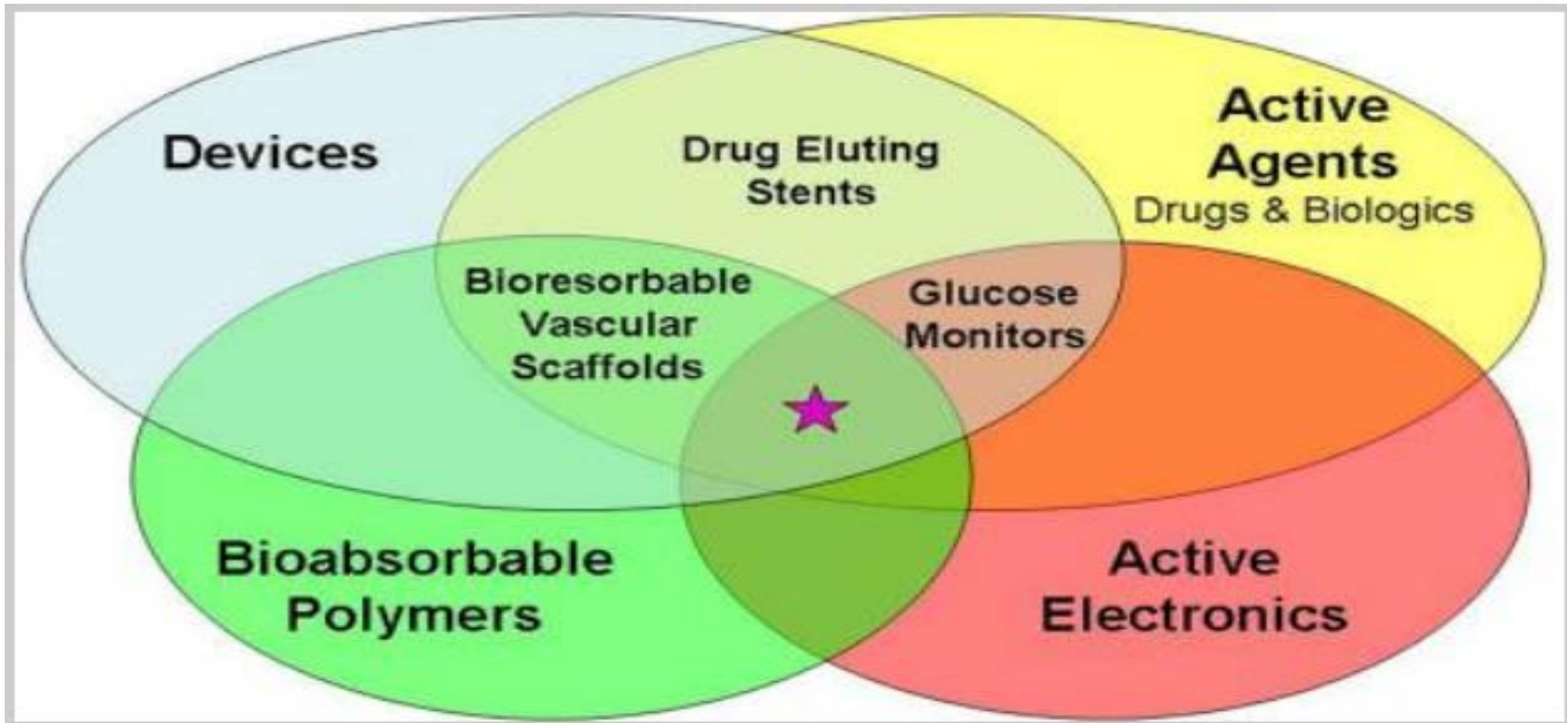
- assessing potential to cause a mutation which could lead to a tumor.

Implantation

- gross and microscopic examination of a device in contact with bone or tissue.

Leachability, Extractability testing.....
Increased Regulatory Environment.....

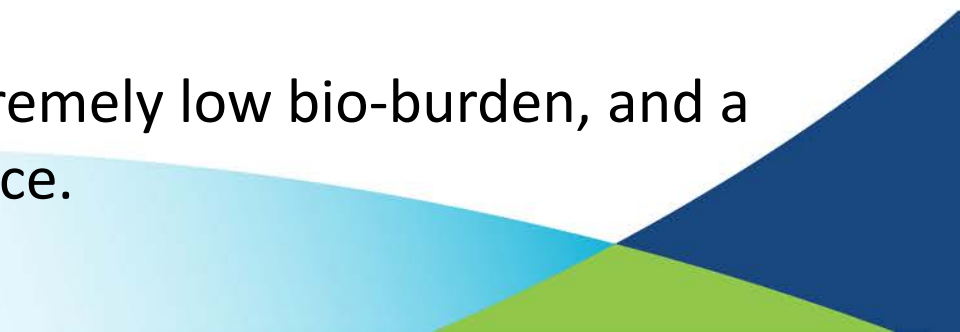
Medical device, Pharmaceutical, Biologic Products



The use of temperature sensitive bio-resorbable polymers for timed release of active agents continue to emerge, including devices that utilize active electronics.

Common to all of these medical product sectors with their sensitive materials is the need for safe, robust, cost-effective sterilization.

Some Trends in Health Care

- Growth in single-use combination type drug, biological, electronic and device products.
 - Drug eluting stents which carry multiple drugs, including infection control, pain control, and regenerative medicines.
 - Successful irradiation of combination products requires fresh thinking.
 - Products likely have an extremely low bio-burden, and a resulting tight dose tolerance.
- 

Novel Sterilization Approaches

- If EO and radiation are incompatible with a combination device, utilization of novel technologies may be a path forward.....
 - If oxidizing agents like hydrogen peroxide, ozone, and chlorine dioxide are compatible with product materials, these modalities have the benefit of processing close to room temperature.
 - Nitrogen dioxide sterilization is being developed; its mode of kill and material degradation is nitration so it may offer promise for additional materials.

Novel Sterilization Approaches

- If EO and radiation are incompatible with a combination device, utilization of novel technologies may be a path forward.....
 - Alternatives are not high-volume technologies, and may be expensive. BUT they may be less expensive and provide higher patient safety profile than aseptic processing.
- Other possibilities:
 - Peracetic Acid Vapor Dry Heat
 - Hydrogen Peroxide
 - Peracetic Acid Vapor
- Newer technologies, smaller volume processing, but may offer the best alternative for a new device...

Challenges for Aseptic Processing

- Validation of process
 - Sterilization of processing equipment
 - Controlled access to aseptic area
 - Measurement of Sterility Assurance Level (SAL)
 - Costly process and potentially risky
- FDA: Seek terminal sterilization wherever possible
- BUT...Aseptic manufacturing is an accepted and established method.

Terminal Sterilization Benefits

- Benefits of EO and radiation are well established....
- Low Cost of Evaluation During Developmental Process.
- Potential Sterilization Cost Savings.
- Ease of Process Validation to a Sterility Assurance Level of 10^{-6} .

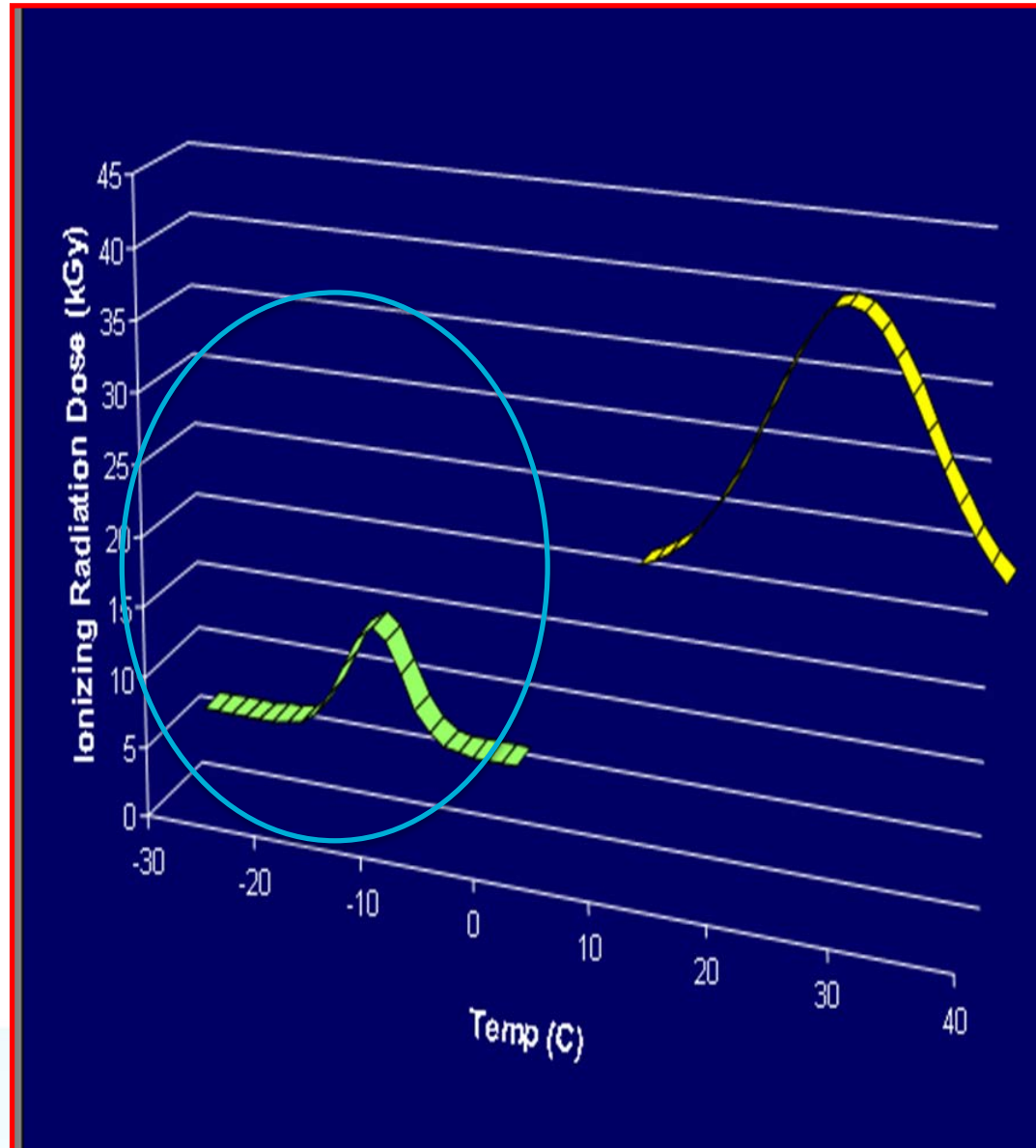


Terminal Sterilization & Pharma: Challenges

- Radiation easy to validate but has challenges
 - Must be decided in “Discovery” stage of pharmaceutical life cycle
 - Scientists/Engineers must be aware of the impact on sterilization
 - Time from fill to terminal sterilization is critical
 - Some Pharma products may support microbial growth
 - Extremely low doses required for most products
 - Straightforward in practice, difficult for some large-scale facilities
 - High processing temperatures may impact the API
 - Radiation compatibility of the API needs to be assessed

The Future is Here

- Increasing product & process complexity
- Requirement to protect bio-actives
- Free radical scavengers
- Low temperature irradiation
- Need for non-traditional approaches to sterilization
- Aggressive development time lines for introducing new products
- Bio-absorbable materials less tolerant to sterilization than metallic counterparts



Mitigation of Radiation Challenges

- Utilize Specialized Equipment to provide unique irradiation capability to deliver precise and low doses.
- Expedited services provide capability to irradiate product immediately to prevent micro growth.
- Use modified environments for the irradiation of unstable products.
- Use Sterilization Scientists with extensive years of experience developing sterilization methods.

New Publication



white paper

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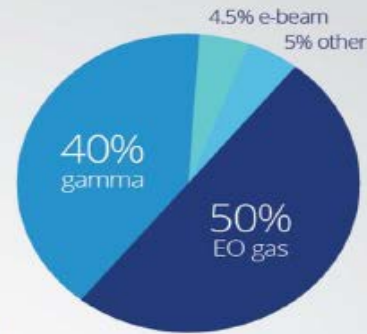
- Descriptions of each technology
- Modality Comparison
 - Suitability
 - Equipment
 - Economics
 - Environment
- Every attempt to ensure impartiality
- WP is available at www.iaglobal.com

New WP – Comparison of Technologies

TABLE 1:
FACTS AT-A-GLANCE

US \$4.69B ACTUAL VALUE GLOBAL STERILIZATION MARKET | 2016
US \$6.93B FORECASTED VALUE GLOBAL STERILIZATION MARKET | 2021

Source: MarketsandMarkets, December 2016



breakdown
of the
sterilization
market

Source: iia

sterilization market is dominated
by North America
followed by Europe, then Asia, then rest of world

Source: MarketsandMarkets, December 2016

'offsite' or
'contract'
sterilization
market
ACCOUNTS FOR
THE LARGEST SHARE
OF THE MARKET
IN 2016

Source:
Medical Design and Outsourcing,
August 2016

US \$140B
VALUE OF US MEDICAL
DEVICE MARKET IN 2015

45%
US MARKET SHARE OF
GLOBAL MEDICAL DEVICE
MARKET IN 2015

US \$45B
VALUE OF US EXPORTS
OF MEDICAL DEVICES
IN 2015

Source: International Trade Administration, May 2016

Summary

- Technology & Innovation will continue to be A Key Force in Healthcare.
- Effective radiation sterilization of combination products and pharmaceuticals are happening today.
 - The selection of the irradiation conditions needed to help maintain its functional properties.
 - Customized solutions (modified atmospheres).
 - Effective radiation sterilization techniques provide a safe and effective drug/product.
 - New methods for establishing a sterilisation dose to minimise radiation damage of the product.
 - Careful evaluation of alternative sterilization techniques


Human Tissues and Biologics

Chronology of Tissue Irradiation

– Past

- Initial studies in 1950s and 1960s
- Standard processing techniques
- Outcome – Poor mechanical results

– Recent: 5 to 10 Years

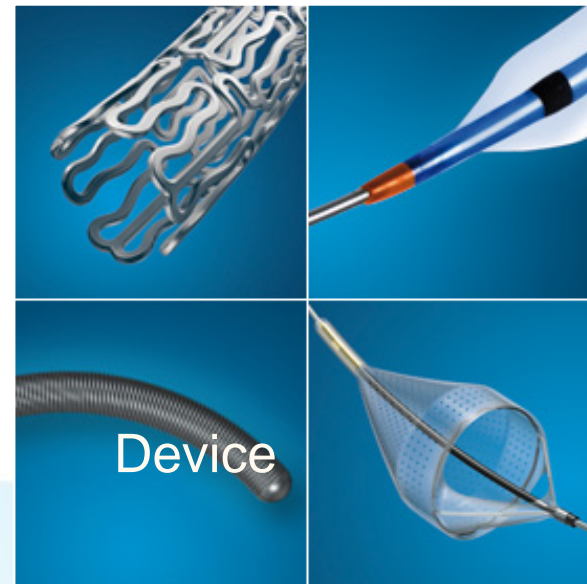
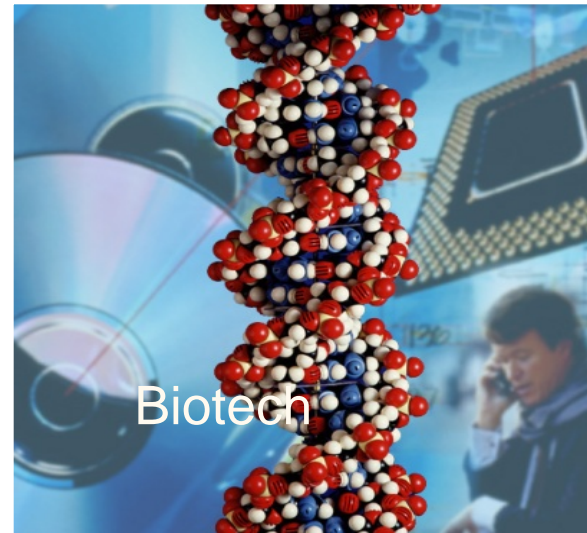
- Reducing the minimum dose requirements
 - Control Environmental conditions during irradiation (and pre/post) and/or use radio-protectants
- 

Human Tissues and Biologics

- Lower temperature irradiations used to minimize mechanical degradation
- Dry ice irradiations to Low temp chamber

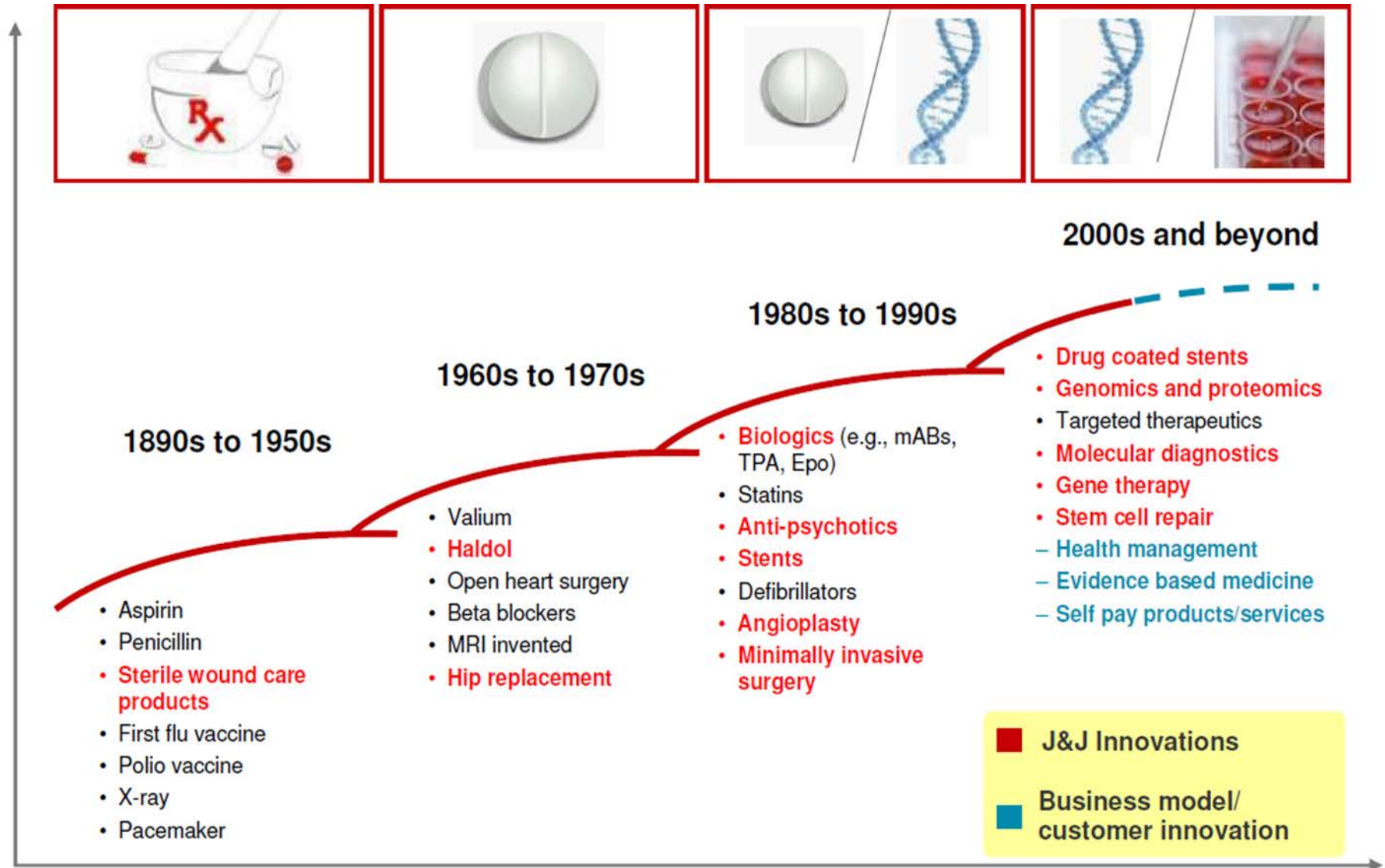


Technology Convergence in Medical Devices

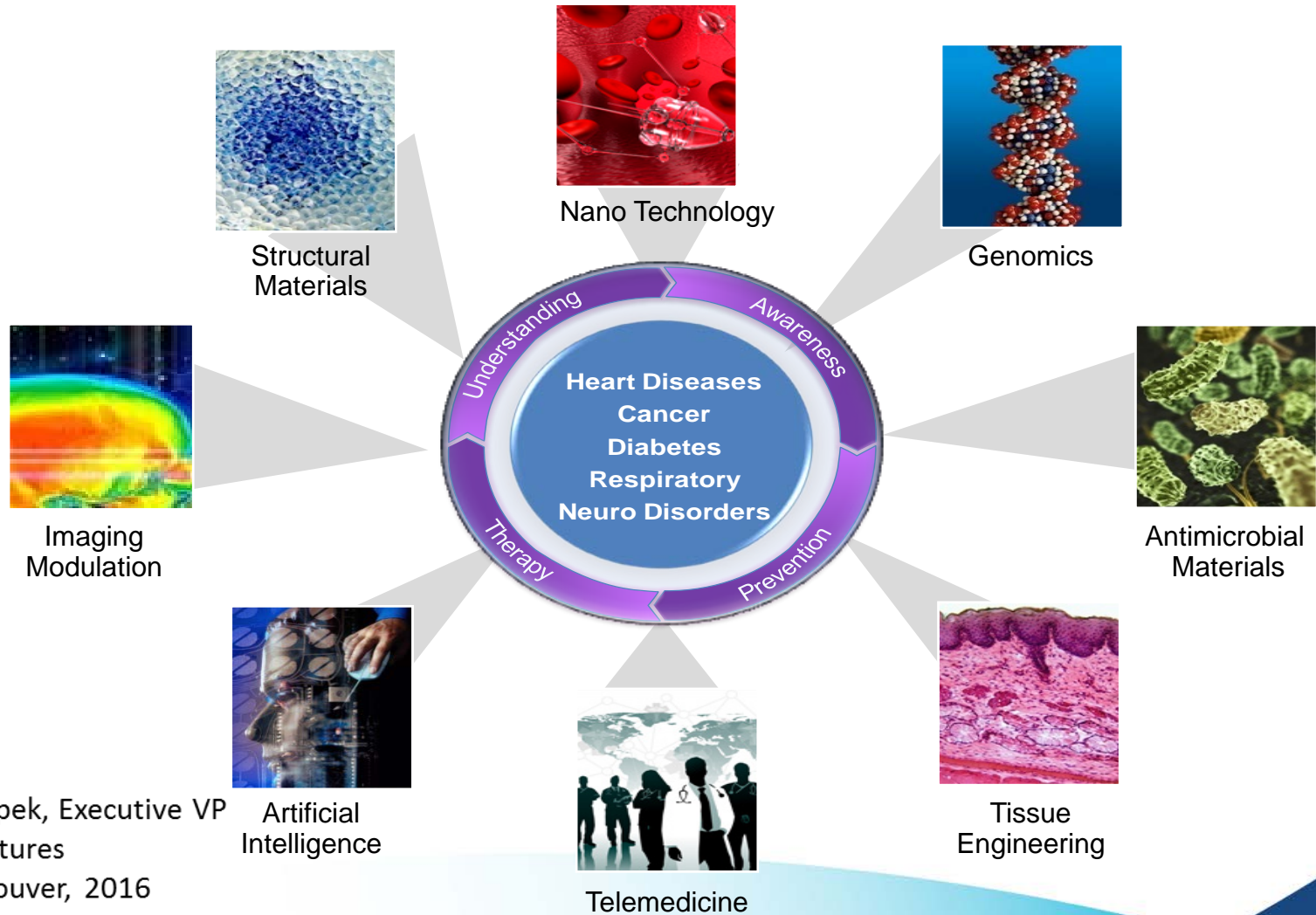


Technology & Innovation: A Key Force in Healthcare

Source: JnJ IMRP Conference



Technology Advancements Drive Next-Generation Integrations



John M. Capek, Executive VP
Abbott Ventures
IMRP, Vancouver, 2016

Challenges to Technology Innovation

Cost Pressures



Government restrictions and shift to consumers

Globalization



Adoption of reference-based pricing
(establish baseline product that all competitors are
reimbursed against)

Patent/IP Law



Emerging market intellectual protection laws

**Premium
Reimbursement**



Health economics and cost effectiveness
required beyond efficacy and safety

Pillars of Public Health



Who Supports Food Irradiation?

- *World Health Organization*
- *Canadian Medical Association*
- *American Medical Association*
- *Centers For Disease Control (CDC)*
- *American Dietetic Association*
- *Institute of Food Technologists*
- *American Council on Science and Health*
- *U.S. Food and Drug Administration*
- *American Public Health Association*
- *United Nations*

- ***Pasteurization***

- ***Immunization***

- ***Chlorination***

- ***Food Irradiation***

Source: Dr. Michael Osterholm

Gamma Sterilization Of Pharmaceuticals

– Case Studies:

- Human Tissues & Biologics
- Bone Grafts
- Virus Inactivation

