Agenda

1. Medical Device Development Roadmap
2. Local Development Roadmap Challenges
3. Financing Requirement
4. Personal Experience
5. Global Healthcare Challenges
6. Summary
A Basic Roadmap

Medical Device Development

From Prototype to Regulatory Approval

Aaron V. Kaplan, MD; Donald S Baim, MD; John J Smith, MD, JD; David A Feigal, MD; Michael Simons, MD; David Jefferys, MD; Thomas J Fogarty, MD; Richard E Kuntz, MD, MSc; Martin B. Leon, MD

Circulation. 2004; 109:3068-3072

Based on the first Dartmouth Drug and Device Development Workshop
- Woodstock VT. October 2003
Idea Generation, Invention

Very few new ideas come out of large medical device companies

More typically originated with *physician* and/or *engineer inventor*

They initiate the patent process

- Provisional (must be converted after 1 year)
- Utility
- International

Build (or commission building) of prototypes
Invention and Development

Small Engineering team

Preliminary bench testing

Build-test-fail-redesign (multiple cycles)

Establish close collaboration with small number of leading physicians in the field

Develop basic market analysis, business plan
Initial Clinical Testing

Design concept frozen
Larger engineering team assembled (10-20)
Broader set of GLP tests performed

*Clinical and regulatory consultants* brought in

Initial *clinical* strategy formulated

- IDE (PMA vs 510k clearance) vs HDE
- Location of FIM and pilot testing (usually OUS) set
- Preliminary discussion of pivotal trial design
  - Superiority vs Non-inferiority, control groups, endpoint

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# Start-Up Value Creation Process

## Milestone Based Planning

<table>
<thead>
<tr>
<th>MILESTONE</th>
<th>Seed Concept 6-12 months</th>
<th>First Round Product 12-18 months</th>
<th>Second Round Regulatory 12-36 months</th>
<th>Third Round Distribution 12 – 36 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>MANAGEMENT</td>
<td>Project Leader</td>
<td>CEO</td>
<td>CEO w/Full Team</td>
<td>CEO w/Full Team</td>
</tr>
<tr>
<td>MARKETING /SALES</td>
<td>Assessment</td>
<td>Market Entry Strategy Define</td>
<td>OUS Distribution Underway</td>
<td>Launch US Distribution</td>
</tr>
<tr>
<td>PRODUCT DEVELOPMENT</td>
<td>Proof of Concept</td>
<td>Product Complete</td>
<td>Next Generation Underway</td>
<td></td>
</tr>
<tr>
<td>CLINICAL</td>
<td>Thought Leaders Identified</td>
<td>Study Underway</td>
<td>Study Completed</td>
<td>Major Company Acquisition, Quality work, Commercialisation</td>
</tr>
<tr>
<td>REGULATORY</td>
<td>Path Outlined</td>
<td>Clear Regulatory Path</td>
<td>FDA Approval</td>
<td>Risks</td>
</tr>
</tbody>
</table>

- **Value**
- **Revenues**

- **Risk 1:10**

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COMMERCIALISATION OF EARLY STAGE INNOVATION: ENTITIES INVOLVED

1 Ideation team
   Typically in public sector research performers (PSRPs) including RIs/IHLs, clinical institutes

2 Early Stage Start ups

3 Late stage start ups & SMEs

Examples:

Project teams within

- NUS
- National Heart Centre Singapore
- M.E.R.C.I
- Nanyang Technological University
- SERI
- Singapore General Hospital SingHealth
- D.D.O.
- CHOCOLATE
- amaranth medical
- EndoMaster
- AIT biotech
- IVANTIS
- Biosensors International
- TriReme Medical
## Commercialisation of Early Stage Innovation: Expertise Involved

<table>
<thead>
<tr>
<th>Ideation</th>
<th>POC</th>
<th>POV</th>
<th>Early Series Funding</th>
<th>Late Series Funding</th>
<th>Exit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial</td>
<td>Clinical</td>
<td>Productisation</td>
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</tbody>
</table>

### Deliverable: Develop business plan and model, project plan and timeline for start up stage
- Start clinical and market validation.
- Conduct IP landscape review and strategy.
- Initiate reg & reimbursement, sales & distribution strategy.

### Deliverable: Identify clinical pathway
- Articulate clinical needs.
- Validate clinical needs.

### Deliverable: Develop working prototype
- Develop working prototype & engineering specs.
- Conduct design risk analysis.
- Initiate design for manufacturing & QMS strategy.

### Deliverable: Execute project plan for early stage of biz and fund raising
- Complete clinical and market validation.
- Do fund raising.
- Do patent reviews.
- Finalise reg & reimbursement strategy.
- Finalise sales & distribution strategy.

### Deliverable: Finalise clinical validation plan and determine end points
- Assemble Scientific & Medical Advisory Board.
- Conduct pre-clinical and clinical coordination work.

### Deliverable: Reach design freeze stage (design for manufacturing and assembleability)
- Conduct design risk analysis.
- Reiterate working prototypes.
- Design for manufacturing processes and engineering.
- Begin QMS work.

### Deliverable: Demonstrate effective biz ramp up
- Do fund raising.
- Conduct IP filing & management.
- File for reg submission & post-market surveillance.
- Pursue & update reimbursement strategy.
- Execute product branding, market launch & extend market reach.
- Ramp up sales & distribution channels.

### Deliverable: Continue clinical validation

### Deliverable: Scale up manufacturing & improve product pipeline
- Sustain engineering for existing products and manufacturing processes.
- Improve product pipeline.
- Update design control & quality audits.
COMMERCIALISATION OF EARLY STAGE INNOVATION: JOB FUNCTIONS INVOLVED

1. Ideation team
   - Typically in RIs/IHLs, Clinical institutes
   - Deliverable: Develop business plan and model, and project plan and timeline for start up stage
     - Project manager (Supported by 1-2 men team)
   - Deliverable: Identify clinical pathway
     (typically outsourced)
     - Clinical PI
     - Clinical development specialist
   - Deliverable: Develop working prototype
     - Core team of technical/ productization engineers

2. Early Stage Start ups
   - Deliverable: Execute project plan for early stage of business & fund raising
     - Early stage CEO
       (Supported by 1-2 men team)
     - Fund raising manager
     - IP filing & mgmt specialist (typically outsourced)
     - Pricing & Reimbursement specialist
     - In Singapore: Functions typically done by early stage CEO
     - CFO for fund raising
     - In Singapore: Functions typically done by one individual

3. Late stage start ups & SMEs
   - Deliverable: Demonstrate effective biz ramp up
     - Late stage CEO
     - Business Dir to execute reimbursement strategy, pdt branding, & ramp up sales & distribution
     - CFO for fund raising

- Deliverable: Finalise clinical validation plan, and determine end points
  (typically outsourced)
  - Clinical development specialist
  - Clinical trial coordinator

- Deliverable: Reach design freeze stage, (design for mtg and assembly)
  - Core team of technical/ productization engineers
  - QMS specialists (typically outsourced)

- Deliverable: Scale up manufacturing & improve product pipeline
  - QMS specialists
  - Core team of technical/ productization engineers
  - Manufacturing Operations personnels
PROPOSED INTERVENTIONS:
“QUALITY” OF PROJECT MANAGERS & EARLY STAGE CEOs

THEORY + EXPERIENCE + MENTORSHIP

Existing programs such as Singapore-Stanford Biodesign program, NUS LLP

Existing incubators & accelerators as potential receptacles to offer local on-the-job training.

Various agencies have their own set of advisors/expert panels.

Intervention #1
Entrepreneurship Fellowship
Support for candidates to undergo on-the-job training in overseas locations (e.g. leading incubators, start-ups)

Intervention #2
Panel of mentors
Group of local and overseas experts to serve as a common resource to mentor local project managers and early stage CEOs
## Typical MedTech Enterprise Funding Model in the U.S

### Class II Devices - US FDA 510(K) Clearance / CE MDD Pathway

<table>
<thead>
<tr>
<th>Key Characteristics</th>
<th>Pre-Seed</th>
<th>Seed</th>
<th>Early-Stage</th>
<th>Mid-Stage</th>
<th>Growth</th>
<th>Pre-IPO</th>
</tr>
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<tbody>
<tr>
<td>Develop &amp; evaluate prototype</td>
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<tr>
<td>Engineering Specification</td>
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<td>Design verification &amp; validation</td>
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<tr>
<td>Design risk analysis (dFMEA)</td>
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<tr>
<td>Design for manufacturing &amp; assembly (DFMA)</td>
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<tr>
<td>Clinical validation</td>
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<tr>
<td>Design freeze</td>
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<tr>
<td>Design history file (DHF) completed</td>
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<tr>
<td>Pilot manufacturing</td>
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<td>QMS certification</td>
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<tr>
<td>CE and FDA certification</td>
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<tr>
<td>Manufacturing scaling-up</td>
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<tr>
<td>Form sales team and appoint distributors</td>
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<tr>
<td>Product branding</td>
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<tr>
<td>Expansion of sales force and distribution network</td>
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<tr>
<td>Reimbursement Success</td>
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</table>

<table>
<thead>
<tr>
<th>Round</th>
<th>Pre-Seed</th>
<th>Seed</th>
<th>Early-Stage</th>
<th>Mid-Stage</th>
<th>Growth</th>
<th>Pre-IPO</th>
</tr>
</thead>
<tbody>
<tr>
<td>~ Quantum</td>
<td>500k – 1mil</td>
<td>&lt; 5mil</td>
<td>5-10mil</td>
<td>10-15mil</td>
<td>20-30mil</td>
<td>30-50mil</td>
</tr>
<tr>
<td>Revenue</td>
<td>Pre-Revenue / 1-2mil</td>
<td></td>
<td></td>
<td>&lt;10mil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>Year 1-3</td>
<td>Year 3 - 6</td>
<td>Year 6 - 9</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Valuation</td>
<td>Value less than ~25mil since clinical impact and ability to commercialise or license has not yet been established</td>
<td>Value of ~25 -100mil due to traction in commercialisation and a vision of sustainability, synergy and licensing</td>
<td>Value of ~100mil – 2bil</td>
<td></td>
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</tr>
</tbody>
</table>

- Focus on Class II devices (broadest spectrum of devices) where MedTech SMEs can compete.
- Class I devices are usually exempted from product registration; and
- Class III devices are usually MNCs’ play.
# Case Studies: Successful MedTech Companies – Proxy Companies for reference

<table>
<thead>
<tr>
<th>Company</th>
<th>Description of Business Activities</th>
<th>Regulatory Pathway</th>
<th>First Funding Date</th>
<th>Date of IPO</th>
<th>Total Funding</th>
<th>IPO Market Cap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Inc</td>
<td>Proprietary automated anastomotic systems used by Surgeons during coronary artery bypass surgery</td>
<td>510k</td>
<td>1997</td>
<td>2006</td>
<td>50mil</td>
<td>98mil</td>
</tr>
<tr>
<td>Conor Medsystems Inc</td>
<td>Drug-eluting stents for the treatment of restenosis</td>
<td>510k</td>
<td>2000</td>
<td>2004</td>
<td>78mil</td>
<td>409mil</td>
</tr>
<tr>
<td>Micrus Endovascular Corp</td>
<td>Implantable and disposable medical devices for the treatment of cerebral vascular diseases</td>
<td>510k</td>
<td>1996</td>
<td>2005</td>
<td>59mil</td>
<td>151mil</td>
</tr>
<tr>
<td>Xtent Inc</td>
<td>Customizable Drug-Eluting Stent (DES) systems for the treatment of coronary artery disease</td>
<td>510k</td>
<td>2002</td>
<td>2007</td>
<td>46mil</td>
<td>376mil</td>
</tr>
</tbody>
</table>

Sources: Stanford Biodesign, VentureXpert, VentureSource
Personal Experience - CanDia 5

CanDia5 is the World’s first and only “point of care” rapid test kit to detect Vulvo Vaginal Candidiasis, commonly known as thrush.

The worldwide market is estimated in excess of US$220 million in Ethical and Retail sectors.

CanDia5 is CE approval.

80% of worldwide IVD sales reside within US, Europe (Top 5) and Japan.
CanDia5- Product Positioning

CanDia5® will be promoted as a screening test for VVC during Pregnancy.

- This is because pregnant women are at high risk of developing VVC during their pregnancy (13% prevalence)

- 10-20% of pregnant women are asymptomatic

- VVC during pregnancy is significantly associated with intrauterine growth retardation[1].

- Recent evidence has also shown that screening and treatment of VVC during pregnancy significantly reduces the prevalence of preterm labour[2].

CanDia5® can be used as an accurate test aiding doctors in the diagnosis of Recurrent VVC

- Most women of reproductive age will suffer from one or more episodes of VVC
- Up to 5% of healthy women of reproductive age may suffer from recurrent VVC, which is defined as 4 or more episodes per year[3].
- Symptoms of VVC are non-specific and neither self-diagnosis, nor diagnosis by a physician is reliable without laboratory confirmation.

Realty: Product Development Challenges

- Basic Research Discovery
- Technology Development
- Patenting

Valley of Death 1

- Product Design
- Clinical Trials
- Product Development
- Regulatory

Valley of Death 2

- Market Creation
- Re-imbursement

Technology Development

Product Development

Commercialization
Healthcare trends

**Patient-centric care**
Better health for more people at lower cost

**Towards wellness and prevention**
From post-symptomatic diagnosis to pre-symptomatic screening
Improved access through telehealth

**Clinical convergence**
Diagnostic tests (in vivo and in vitro)
Diagnosis linked to therapy
Convergence of pharma / diagnostic industries

**Productivity and ‘cost-out’ driven**
Reimbursement pressure on providers

**Information driven**
Payors demand rigorous cost/benefit analysis
Accessible and actionable patient information
Need for a fundamental change...

AGING POPULATION • PEOPLE WITH MULTIPLE DISEASES TREATMENT COSTS • PRODUCTIVITY LOSS

Cancer
1 in 3 people will get cancer

Heart Disease
1 person dies from CVD every 33 seconds

Brain Disorders
1 in 8 people 65 & older has Alzheimer’s

1Cancer Research UK  2American Heart Association  3Alzheimer’s Association
# Top challenges in developed markets

## Drivers and issues

<table>
<thead>
<tr>
<th>Revenue</th>
<th>Cost</th>
<th>Quality</th>
<th>Access</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>USA</strong></td>
<td>Declining revenues and shift from fee for service to Population Health Management, accountable care</td>
<td>More insured and aging population/chronic disease on rise</td>
<td>Care is not coordinated and fragmented. Seamless IT/digital requirements escalate</td>
</tr>
<tr>
<td><strong>Nordics</strong></td>
<td>Constrained by limited availability of public funds</td>
<td>Cost containment thru increased efficiency of resources</td>
<td>Incentives to better integrate different levels of care and IT requirements increase</td>
</tr>
</tbody>
</table>

HIMSS Leadership Survey, Senior IT Executive Results, February 21, 2012
Top challenges in emerging markets

Drivers and issues

<table>
<thead>
<tr>
<th></th>
<th>Revenue</th>
<th>Cost</th>
<th>Quality</th>
<th>Access</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>Growing private, state/fed health insurance, medical tourism: 28% CAGR</td>
<td>Critical need to update/expand HC technology &amp; infrastructure</td>
<td>26 states &amp; one federal district with varying economics and regulations</td>
<td>Access is improving, demand increasing with need for staff, technology, IT</td>
</tr>
<tr>
<td>India</td>
<td>Inefficiencies limit patient throughput and revenue, driving high prices</td>
<td>Patients spend significant portion of income on private healthcare for advanced disease</td>
<td>Informatics, analytics solutions for population management</td>
<td>Expansion of small-to mid size hospitals, care centers, provider training</td>
</tr>
<tr>
<td>Middle East</td>
<td>Need regulatory, informatics, payment framework for private sector $, private insurance</td>
<td>Rapidly increasing costs due to exploding volume of expensive chronic patients</td>
<td>Lack of skilled providers at all levels; High turnover rate due to expats</td>
<td>Lack capacity to provide services to rapidly increasing multi-complex chronic disease patients</td>
</tr>
</tbody>
</table>

Reference: E. Mediterranean Health J “Need for Building capacity to prevent chronic diseases in North Africa and The Middle East”; Booz & co “Getting a handle on Chronic Disease Health Management Services in the GCC Region”; Harvard J. of Middle East politics & Policy “Emerging trends in Middle Eastern Health Policy”

Questions:

• Would a device designed & manufactured in Singapore be applicable to the rest of the world?
• If not, where do we develop local products?
• How do we develop local products?
• Will local products have utilization elsewhere?
Summary

• Medical Device Development is a long journey
• Starting with focusing on medical needs, but also need to understand market demand
• Challenges in commercialization talent and financing
• Need strategic locations for product definition, development, and commercialization
• Products developed in one location can be applicable to many other locations