Medical Device Development: Thinking Globally, Acting Locally

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Strategic Perspective
Introduction: Medtech and the Healthcare Landscape

The global healthcare and healthcare service market will maintain steady growth due in large part to an aging population that is living longer and to improved healthcare services in emerging markets that include China, Brazil, India, Japan, Israel, and South Korea, among others. It is interesting to note that counterto trends seem to be developing in the medical device space; for example, hospital utilization of medical devices has slowed significantly, reimbursements continue to tighten, and there was a first-time global decrease (5%) in US premarket approvals (PMAs) in 2012, a trend that continued into 2013. There were also fluctuations in investor healthcare spending across 2012, drops in mergers & acquisitions deal value and deal counts, and a device tax that is adding to the squeeze.

Overall, Medtech growth has been solid, with consistent 5%-6% annual growth and global annual revenues projected to nearly double, from $270 billion/year to $500 billion/year, over the next 10 years. Medtech projected revenue growth is expected to outperform Pharma revenue growth (5% vs 3.8%) over the 5-year period ending in 2018, with in vitro diagnostic devices (IVDs), cardiology devices, and diagnostic imaging devices in the top three revenue slots. Medtech R&D spending is steady at about 3%-4% year-on-year growth, although regulatory affairs and quality assurance expenses are growing 3-5 times the budgets Medtech saw 5 years ago due to the ongoing challenges for manufacturers to get new technology into global markets and to keep those products on the market.

Growth in the global Medtech space is healthy, with opportunities expanding beyond traditional markets (US and EU) into the rest of the world (Table 1). North American and European markets still predominate in the top ten, but key Asian and South American markets are on the rise, both on their imports and exports. Incorporating international and emerging markets at an early stage of product development is critical for long-term success in getting to market but also in bringing regulatory and quality costs down by getting started smart. From a Medtech development standpoint, thinking globally when developing the “get-to-market” strategy for your device product needs to become the rule rather than the exception. Large companies are already planning globally, and even they find it challenging, so it is particularly challenging for startup and medium-sized companies due to a lack of the right resources or the best strategy.

Understanding market opportunities from a regulatory, reimbursement, and healthcare delivery perspective, as well as understanding market fluctuations, are the first steps in planning a global strategy—what is the market doing now and what may it be doing in the future? The reimbursement and regulatory landscape is equally critical. Just within the US-EU axis, a Class II device in the US might be Class III in Europe, with different regulations and requirements across the whole development lifecycle. Likewise, in China device approvals may require additional endpoints, and retrofitting your data could cause years of delay.

Market Strategy

An innovative product starts with a great idea and the market niche to make the product viable (eg, unmet patient need, emerging illnesses/conditions, shortcomings with current therapies and products). Differentiation of your product is key (Figure 1). The first question to ask is, How will I compete in this space? Likewise, careful analysis of overall market size, specific market opportunities, competitive landscape, reimbursement challenges, basic health economics, and regulatory challenges are indispensable. You can count on the fact that unrealistic expectations will be exposed sooner rather than later (eg, “We expect 45% market share in 3 years against industry giants.”) So, in addition to starting smart with a global eye, you also need to be a realist.
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Table 1. Shifts in Global Healthcare Market Rankings, 2003-2013

<table>
<thead>
<tr>
<th>2003 RANK</th>
<th>2009 RANK</th>
<th>2013 RANK</th>
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<tbody>
<tr>
<td>1. UNITED STATES</td>
<td>UNITED STATES</td>
<td>UNITED STATES</td>
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<tr>
<td>2. JAPAN</td>
<td>JAPAN</td>
<td>JAPAN</td>
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<tr>
<td>3. GERMANY</td>
<td>FRANCE</td>
<td>CHINA</td>
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<td>4. FRANCE</td>
<td>GERMANY</td>
<td>GERMANY</td>
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<tr>
<td>5. ITALY</td>
<td>CHINA</td>
<td>FRANCE</td>
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<tr>
<td>6. UNITED KINGDOM</td>
<td>ITALY</td>
<td>ITALY</td>
</tr>
<tr>
<td>7. SPAIN</td>
<td>SPAIN</td>
<td>SPAIN</td>
</tr>
<tr>
<td>8. CANADA</td>
<td>UNITED KINGDOM</td>
<td>BRAZIL</td>
</tr>
<tr>
<td>9. BRAZIL</td>
<td>CANADA</td>
<td>CANADA</td>
</tr>
<tr>
<td>10. CHINA</td>
<td>BRAZIL</td>
<td>UNITED KINGDOM</td>
</tr>
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</table>

Source: Business Monitor International.

Other key questions are:

- What revenue can I reasonably expect, based on the average sale price of my product vs projected cost of goods?
- Is my product affordable in the intended market?
- Will it be and stay reimbursed at expected levels?
- What market share would constitute success?
- How strong is my clinical data?
- Is my intellectual property well protected? Am I willing or able to fight to protect this? The ability to protect intellectual property in some countries can be greatly influenced by proactive steps—in China, for example, simply registering your trademark can make a significant difference.

Once a device is on the market, post-market data and health economics can help differentiate your product more than ever—for example, decreased hospital stays or eliminating the need for additional medications or procedures is part of the argument that sets your device apart beyond a reimbursement story.

Figure 1. Differentiating your product. Clinical data are often the number one driver in product differentiation and value.
Factors Impacting Medical Device Differentiation in the Market
Understanding and optimizing your product differentiators goes a long way toward having a successful get-to-market strategy. Another key to success is a solid global approach. Most savvy investors and senior leadership will expect a global strategy as part of the get-to-market approach from R&D, and going to the US and EU first before looking globally is no longer enough to gain funding or company buy-in. All products are unique and what may work for one technology could be classified completely differently in the next market. In some cases approval in the US may allow for quick access into other markets with low barriers to entry once approved. Begin thinking about these possibilities early to optimize the potential—and in many cases, to reduce investment risk.

Managing the Product Development Effort
Strong teams who understand the development process (Figure 2) and have good cross-functional communication are essential to effective device development. Mistakes and challenges can and will occur during various steps in the medical device development lifecycle. Challenges can be the result of errors in strategy (eg, single market rather than global market strategy), regulatory (eg, poor strategy for stating the indication for your product), or even reimbursement-related (eg, realizing too late that no reimbursement code exists, causing delays in funding and/or adoption in the marketplace). Reliance on a singular strategy will at best be incomplete and in most cases will fail to reach approval, much less revenue. Get-to-market success is most often associated with well-planned market analysis that encompasses global reimbursement considerations, global regulatory considerations, a strong management team, good intellectual property (IP) planning, strong partners, and trustworthy communication at every phase.

Figure 2A. Device development lifecycle.

Figure 2B. Arrows depict the reality of the device development timeline, in that the timeline can be affected by iterations during development. While these iterations are a natural part of the process, the ability to rapidly find problems and solutions within your teams is what separates success from failure.
Figure 3 is a high-level depiction of development lifecycle phases that indicates disciplines, milestones, and activities. Aligning a get-to-market strategy across all disciplines and phases that can speak to global opportunities is optimal.

### Figure 3. Medical device development: key activities within each phase

<table>
<thead>
<tr>
<th>Concept/Feasibility</th>
<th>Design Validation &amp; Preclinical</th>
<th>Clinical</th>
<th>Market Approval</th>
<th>Post-Market</th>
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</thead>
<tbody>
<tr>
<td>• Global regulatory assessment</td>
<td>• Preclinical research &amp; model development</td>
<td>• Study design &amp; management</td>
<td>• Global marketing applications</td>
<td>• Post-market clinical trials &amp; registries</td>
</tr>
<tr>
<td>• Design controls</td>
<td>• Test method development &amp; validation</td>
<td>• Biostatistics</td>
<td>• FDA BIMO Inspections</td>
<td>• Microbiology testing</td>
</tr>
<tr>
<td>• Pre-submission meetings</td>
<td>• Quality systems/quality management</td>
<td>• Data management</td>
<td>• FDA panel meetings</td>
<td>• Sterilization assurance</td>
</tr>
<tr>
<td>• Global regulatory strategy</td>
<td>• Global regulatory strategy</td>
<td>• Report writing</td>
<td>• Packaging validations</td>
<td>• FDA reporting requirements</td>
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<td></td>
<td></td>
<td>• DMC/CEC</td>
<td></td>
<td>• Material characterization</td>
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<td>• Physician training</td>
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<td>• Training seminars</td>
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<td></td>
<td>• IDE submissions</td>
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<td>• Study design &amp; management</td>
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**Incremental vs. Disruptive Products**

Many device products are **incremental** in that they represent refinements or variants of technologies that are already available, such as sharps/needle protection technologies, improved catheters, infusion lines, PICC lines, etc. Other devices are **disruptive**—that is, they represent a new technology, an unmet need, a new material, or an innovation that gives the disruptive product the potential to rearrange the market or even change the practice of medicine—e.g., venous stents, leadless pacemakers, robotic surgical devices, electronic medical records, or phone apps.

Both types of products face similar challenges, although incremental/iterative products are able to rely more heavily on differentiation strategies while disruptive products will likely have a greater burden meeting regulatory and testing requirements because of their innovative, unknown status. Clinical and health economic data are more critical in the approval process of disruptive products, and early and frequent interaction with regulatory authorities will be necessary, particularly if it is wholly unfamiliar and authorities need to be educated on the product’s concept and use. In many international markets, this sort of extended interaction with authorities is difficult to obtain, so it is important to get expert advice on the particular market to fully evaluate the risks. For disruptive products, challenges may also be at the reimbursement level, e.g., if the device/procedure does not fit under an existing reimbursement code. Strong clinical evidence and support from key clinical practitioners will be needed to establish a new code. And as always, looking at global markets is key since the uniqueness and economic premise of your product may not hold up in a foreign context.

**Regulatory Strategy**

Early decisions as to your regulatory strategy impact all decisions downstream, in that your strategy can influence testing, labeling, and clinical requirements. You need to ask about what functional, biocompatibility, or chemical characterization testing would be required to demonstrate equivalency, and likewise about what clinical data are required for regulatory approval. It is also important to understand which regulations pertain to labeling and medical device reporting (MDR). Before submission, frequent regulatory feedback can speed approval, although as noted above this sort of access will likely require expert advice from someone well versed in the intended market(s). But submitting your dossier is often just the beginning of the process and several rounds of discussion may be required before acceptance.
It is essential to work smart from the start and take into account global regulatory/testing requirements from the beginning. Many markets outside of US/EU prefer testing to risk assessments for example—or don’t expect to go to China for an orthopedic product without clinical data, as another example. And remember, regulations on required response times across the globe are constantly changing.

Other Strategies—Points of Note

**Reimbursement Questions**
- Which markets present the best opportunity for your specific indication? Are the regulatory path and indications for use aligned?
- Can approval in country “A” gain you access into several other countries? Is this product reimbursed for use in those countries?
- What are the coverage, coding, and payment processes and related timelines in each market?
- Which markets are the easiest and fastest to receive reimbursement? Revenue? Data?
- Differences between markets: Japan reimbursement is sufficient, but in the US it can be difficult just to break even. Likewise, how healthcare is delivered in China may be significantly different than US/EU.

**Quality/Compliance**
- Quality system compliance is often the most time-consuming and complex component of device registration
- Quality systems must comply with all quality standards, including proper design controls/process controls, proper qualification of suppliers with proper documentation, and review of all local and international requirements
- Do you understand changes regarding quality system audits, which can be unannounced in some markets?
- Most quality systems are too large or nonexistent
- Begin thinking early about how your quality manual will integrate with your manufacturing strategy

**Testing**
- Required testing is essentially the “Validation of Safety”
- Review product standards in all markets
- If targeting multiple markets, consider performing a “gap analysis” of testing requirements across the markets—for example, China uses older versions of ISO standards and also has “Chinese National Standards” that could differ from US/EU or MHLW (Japan) requirements
- Additional testing in parallel or additive to an existing test plan could provide significant long-term savings if the plan is to eventually enter foreign markets
- Understand how your system (made up of various components perhaps) could be tested in its entirety, but understand also that this plan may prohibit you from selling those individual components without significant additional testing (in other words, there is likely a more optimal testing plan!)
- Review all materials in product for proper use and equivalency to predicate
- Disruptive:
  - Alignment of functional studies with regulatory and clinical experts will greatly expedite time to first enrollment, often improves enrollment rates, and of course gets the product to submission sooner
  - Strategic consideration should be given to larger functional studies harmonized with smaller clinical studies
  - In certain foreign markets, discussion and education with government-owned/endorsed testing labs (who don’t have an equivalent in US/EU markets) is vital to success with more disruptive technologies

Strong teams who understand the development process and have good cross-functional communication are essential to effective device development.
Clinical

- The clinical study is the “Validation of your Safety and Efficacy” work thus far
- Typically required by regulators for high-risk products, but may not be for moderate or low risk products
- Path to differentiation—goal is to minimize costs for clinical trials and plan publications to support reimbursement/approval and eventual commercial goals
- Is additional data worthwhile to differentiate from competitors in a crowded market/post-market?
- During clinical trial design, reimbursement strategy and “motivation” of key opinion leaders (KOLs) should be considered—health outcomes and health economics are here to stay and there may be opportunities to consider this during your clinical design

Post-Approval: Manufacturing, Distribution, and Post-Market Strategies

Once a device approaches approval or nears a significant clinical study, manufacturing and distribution scalability come to the forefront. Begin scaling your manufacturing strategy in step with your distribution strategy. Decisions should already have been made about contract vs. in-house manufacturing, taking into account that contract manufacturing organizations (CMOs) or local manufacturers can in many cases expedite your entry into those markets (China, Japan, and Brazil are examples). Optimization of the manufacturing process includes stability/reproducibility of the manufactured product, product compliance, and the ability to introduce process improvements. Are there opportunities to reduce cost of goods sold (COGS) to improve your average sale price (ASP)? Process flexibility is another key to optimization and too often developers don’t plan early enough for this essential discipline.

As for distribution, it is critical to have a strategy for encouraging commercial adoption. You also need to determine if registration in a country can be completed by your potential distribution partner and if this is necessarily what you want, or if a third party would be better. Ask whether adoption will be based on brute sales force, on regional/national distributors, on specialized distributors, on direct-to-patient or over-the-counter sales, and/or on KOLs. Again, a single strategy may not be enough to ensure success or appease investors. These strategies will differ for disruptive products, which may require greater need for sales and physician training for product adoption.

Post-market strategies should include training and ongoing clinical evaluation to further validate patient safety and product efficacy and to support claims and future claims as well as encourage market adoption. It is important to use post-market data to differentiate your technology, evaluate minor product improvements, and publish and promote your product to KOLs. For first-to-market and disruptive products, physician training and sales force training will be a large part of this post-market process.
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Summary
Development: Communication and collaboration across the product development life cycle—among stakeholders, development teams, and development partners—is integral to success. Nothing can be accomplished in a bubble. Aligning your get-to-market strategy across all disciplines is critical, and the earlier the better.

Approval: No product is alike and regulatory, reimbursement, and global market conditions are constantly changing. Expert advice in these disciplines can save mistakes and delays. For investigational devices, convincing clinical data, ideally linked to positive health outcomes, are key to product adoption. Clinical data are the single biggest driver for startup valuation, and more than ever is the driver behind big Medtech stock value. Successful data drive sales and set companies apart.

Reach: Failure to explore global market opportunities at the outset can lead to delays and inefficiencies. Products that eventually show growth will be followed with the decision to move to international markets. This will often lead to the need for additional testing, regulatory, and clinical data. A “Start Smart, Emerging Market” strategy at the outset will more often satisfy investors and Senior Management alike because such a strategy reduces risk through parallel options, and optimizes various testing and clinical requirements. Investors and Senior Management alike want a customized, global development strategy.

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