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Understanding the International Medical Device Regulatory Process

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Topics

- Understanding the three types of countries in terms of regulation maturity; developed, semi-developed, not developed
- Importance of regulatory and marketing strategies
- Building a dossier - some common elements
- Due diligence in terms of additional testing/documentation
- In-country agent/distributor
- Product testing and CB scheme
- Review time & cost
- Preparing for the unexpected
- Case Study - China

Starting Out

- Three types of countries in terms of regulation maturity;
  - Developed – US, EU, China, Brazil, Australia, Canada, Japan
  - Semi-developed – Vietnam, Mexico, Malaysia, Kuwait, Egypt
  - Not developed – Africa, India, Indonesia

Regulatory Strategy

- Must be aligned with marketing and business strategy
- Best to understand market strategy early in the product lifecycle
  - Develop 3-5 year plan
  - Regulatory strategy should be based on marketing/business strategy
  - Some countries registration process can take 1-3 years so time to market is crucial
  - Think parallel, not serial

Initial Launch Strategy

- In order to develop a viable business and regulatory strategy, you must understand your target market, the amount of internal and external resources required, and the amount of reimbursement available
- From a timeline perspective, there can be a several month difference in launching new medical devices into the U.S as compared with the EU
  - The FDA requires evidence of both safety and efficacy of a device
  - European CE Marking only requires proof of safety and that the device performs in a manner consistent with the manufacturer's intended use

Common Regulatory Strategy Options

- Seek Clearance/Approval in the U.S. First
  - Seeking FDA clearance gives medical device companies the advantage of being able to launch and market their products to the largest medical device consumer in the world
  - Additionally, medical device companies can expect more consistent reimbursement, better intellectual property protection, and less foreign competition
- Seek Clearance/Approval Overseas First (Typically EU)
  - The EU is the second largest medical device consumer in the world
- Start Clearance/Approval Process in Parallel
  - Typically this is US and CE Marking
  - Ideal strategy in terms of reducing regulatory risks due to costly delays in the launch of a device, but requires the most resources

Risks and Tradeoffs

- For start-up medical device companies, funding is limited
  - Companies must determine the tradeoffs of their regulatory strategy in order to minimize risks
  - For example, although the CE Marking timeline is faster and the process is predictable, there is no guarantee that the device will be widely accepted by physicians or reimbursable by each government in each European country
  - Additional clinical evaluations and registration might be required in some EU countries to show the efficacy of the device from a marketing perspective
  - The upside is that once a device is CE Marked, subsequent in-country approvals are typically much quicker

Risks and Tradeoffs

- The FDA regulatory process is longer and has a higher burden for safety and efficacy, however;
  - Once a device has received FDA clearance, companies can start marketing their product in the entire U.S.
  - Reimbursement in the U.S., such as Medicare, is more consistent since there is only a single government
  - Some foreign regulatory agencies require a device be registered in the country where the legal manufacturer resides as part of their registration process and final approval
    - Goes back to the company's business and marketing strategy

If Clinical Studies are Required

- A study conducted under an investigational device exemption (IDE) outside the United States and submitted in support of a PMA must comply with the IDE regulation (21 CFR 812)
- A study conducted outside the U.S. which was not conducted under an IDE must comply with:
  - The data constitute valid scientific evidence
  - The investigator has conducted the studies in conformance with the Declaration of Helsinki or the laws and regulations of the country in which the research was conducted, whichever offers greater protection to the human subjects
  - The rights, safety, and welfare of human subjects have not been violated
- A PMA based solely on foreign clinical data may be approved if:
  - The foreign data are applicable to the U.S. population and medical practice;
  - The studies have been performed by clinical investigators of recognized competence; and
  - The data may be considered valid without the need for an on-site inspection by FDA or, if FDA considers such an inspection to be necessary, FDA can validate the data through an on-site inspection or other appropriate means
- Applicants who seek approval based solely on foreign data are encouraged to meet with FDA officials in a pre-submission meeting

Assembly of Documentation

- Building a dossier; some common elements
  - STED - The Summary Technical Document (STED) format for regulatory submissions is a harmonized submission format developed by the Global Harmonization Task Force (GHTF)
    - GHTF disbanded in November 2012; following on GHTF is The International Medical Device Regulators Forum (IMDRF)
  - The STED format is still a valuable tool for international registrations as it is a good way to;
    - Organize common documents that will be part of multiple country dossier submissions
    - Organize technical information in one central repository
    - Only need to complete country specific elements
- The Asian Harmonization Working Party (AHWP) has a final draft of CSDT (Common Submission Dossier Template)

Key Sections of the CSDT and STED

CSDT

Sect.	Heading
3.0	Executive Summary
4.1	Essential Principles
4.2	Device Description
4.3	Design Verification and Validation
4.4	Risk Management
4.5	Labeling
4.6	Manufacturer's Information

STED

Sect.	Heading
6.0 - 6.3	Device Description and Product Specification
7.0	Labeling
8.0 – 8.3	Design and Manufacturing Information (design stages)
9.0	Essential Principles
10.0	Risk Analysis and Control Summary
11.0 – 11.8	Product Verification and Validation
13.0	Declaration of Conformity

National Differences

- Due diligence in terms of in-country contacts
  - In-country agents – most countries require submissions through a person or company that resides in the country
    - This can be either affiliated with your company
    - If not – you will need to select the right in-country agent that understands your product in terms of technology and regulations
  - Distributors – some companies use distributors to register products and distribute product post approval
    - There is a risk in doing this if the distributor does not perform to expectations in terms of revenue, remember the product is licensed in the distributor's name – not your company's name
    - You need to ask yourself; does the potential distributor sell synergistic products? Does the distributor have strong sales and marketing personnel? Do they have qualified in-house regulatory people to help with product registration?
    - Relationships are the key to doing business, so do not sign up distributors that you do not know well. Can you speak the distributor's local language or is their English sufficient to communicate? Does the potential medical distributor understand the notion of "conflict of interest"?
    - For example - Given the large geographic size and population of China and India, you will probably need multiple distributors in each country
  - Due Diligence Audits – virtual or on-site; perform extensive due diligence to find the best medical distributor
- DOC/Consultant – this is a great resource if you are new to the country
  - Ensures vetting process

National Differences

- Due diligence in terms of additional testing/documentation
  - NRTLs – If your product requires product safety testing then you should work with your NRTL from the beginning (design stage)
  - You should define your target markets for the next 3-5 years based on business/marketing strategy (major technical upgrades)
  - Work with the NRTL to test for base standard, national differences and CB Scheme
  - Will save time and money as you launch your product in new countries
  - CB Scheme –
    - Reports and certificates dealing with the safety of electrical and electronic components, equipment and products with national differences
    - There are 52 Member Countries, 65 participating National Certification Bodies and 276 Testing Laboratories
    - Caveat – some countries still require in-country product/safety testing (ex. China)

Preparation & Submission

- You will need to work with in–country personnel and in some cases NRTLs to understand if there are national differences in standards that your company should take into account at the early stages
  - This could mean additional testing or a different design
- In any case, you will want to know as you are working with engineering, marketing, and other functional groups to make informed decisions about entering a specific country
- Be prepared for the unexpected; clinical studies, product testing
- Depending on the your approach either the company, in-country agent or distributor submits the dossier to the government

Time & Money

FDA US	Device Class	Cost	Total Time (avg days)
	Class II (510k)	$4,960.00 ($2,480.00)	90-145
	PMA	$248,000.00 ($62,000.00)	180-270
CE Marking EU	Device Class	Cost	Total Time (avg days)
	Class I (m/s)	$3,000.00	Typically 1-3 days assessment time plus pre-review, device dependent. Typical cost per day $1050-$2000.
	Class IIa	$4,250.00	
	Class IIb	$5,500.00	
	Class III	$7,500.00	
13485	Typical cost is $6000 for the certification by NB. Preparation costs is not included and is dependent on individual company readiness		
HC Canada	Device Class	Cost	Total Time (avg days)
	Class II	$365.00	30
	Class III	$5,255.00	60-75
	Class IV	$12,225.00	75-90

Time & Money

HSA Singapore	Device Class	Cost (Appl & Full Eval Fee)	Total Time (avg days)
	Class A	$25.00	30
	Class B	$4,025.00	160
	Class C	$10,225.00	220
	Class D	$11,900.00	310
TGA Australia	Device Class	Cost	Total Time (avg weeks)
	Class I (m/s)	$535.00	6 to 10
	Class IIa	$820.00	
	Class IIb	$820.00	
	Class III	$1,050.00	
TFDA Taiwan	Device Class	Cost	Total Time (avg months)
	Class 1	$340.00	2 to 3
	Class 2	$1,000.00	4 to 9
	Class 3	$1,170.00 - $1,670.00	12 to 16

Does not include costs or times associated with: establishment registration, other registration costs, ongoing reassessment costs or company preparation costs. In some cases actual costs may be lower if a particular registration can be submitted through an expedited or abridged process in some countries.

Regulations to Consider

- Regulations changing all the time
  - Taiwan - require EP STED as the guideline for product registration in 2014 (already required for Class 3). In addition, application for GMP license by simplified mode is only applied to the EIR issued within 3 years
  - China - nearly all class 2 and class 3 medical devices (including IVDs) are required to do clinical trials in-country
  - Malaysia - medical device regulation came into effect with Act 737, July 2013. A transition period of two years for medical device registration and one year for establishment licensing will be given to the industry before it is fully enforced

Trade Compliance Regulations

- Import/Export Regulations
  - HTS -Harmonized Tariff Schedule is the mechanism by which international tariffs are harmonized (first 6 digits). Importers and Exporters must classify all goods moved across international borders, www.usitc.gov
  - EAR – Department of Commerce Bureau of Industry and Security (BIS) is responsible for implementing and enforcing the Export Administration Regulation (EAR)
    - Need to review components, subassemblies and finished device to ensure it does not contain “dual-use” items
      - Items that have both a commercial and military or proliferation application
      - Review Commerce Control List (CCL) on www.bis.gov
      - Most devices will be EAR99 which, in most cases, does not require a license except if exporting to an embargoed country

Trade Compliance Regulations

- OFAC
  - The Office of Foreign Assets Control (OFAC), Department of the Treasury, administers and enforces economic and trade sanctions based on US foreign policy and national security goals against targeted foreign countries and regimes, terrorists, international narcotics traffickers, activities related to the proliferation of weapons of mass destruction, and other threats to the national security, foreign policy or economy of the United States www.treasury.gov
- Import/Export Trade Management
  - Exports must be screened against restricted party lists, determine license requirements, perform export compliance checks and generate international trade documents prior to shipping
  - Imports must comply with complex country-specific trade regulations, calculate variable duties, taxes and fees, and manage related logistics challenges
  - There are a number of Trade Management software companies that provide expertise in this area
- In some cases companies use a broker to maintain import compliance but it is the company that is ultimately responsible for all import and export compliance activities

Approval

- So now you have clearance/approval from a country – what's next?
- To be successful and hit the ground running - need to think about entire chain from premarket to postmarket
  - Supply chain
    - To/from port of entry
    - Within country distribution
  - Reimbursement
  - Cultural Differences – product name, product model number, advertising, product acceptance, selling strategy, pricing strategy
  - Complaints, vigilance reporting, market withdrawal, recalls, adverse events

Case Study; China

- Product – Endometrial ablation device (Class III)
- Issue: dossier submitted but languishing
  - Worked with in-country agent to determine status with SFDA
  - Additional requirements: clinical, testing, documentation
  - SFDA lacked understanding of device technology and overall procedure by physicians

Case Study; China

- Outcome
  - Conference call and met with SFDA and in-country agent
  - Provide technical detail regarding RF ablation device
  - Provide medical overview of endometrial ablation using RF energy
- Able to provide scientific papers regarding the use of RF energy for endometrial ablation instead of in-country clinical trials
- Provided additional technical specifications and risk analysis regarding the safety of the device
- Product approved within 4 months of the call and visit

Thank You

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