Life Science Opportunity:
Overview & Medical Devices

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Overview of Japan

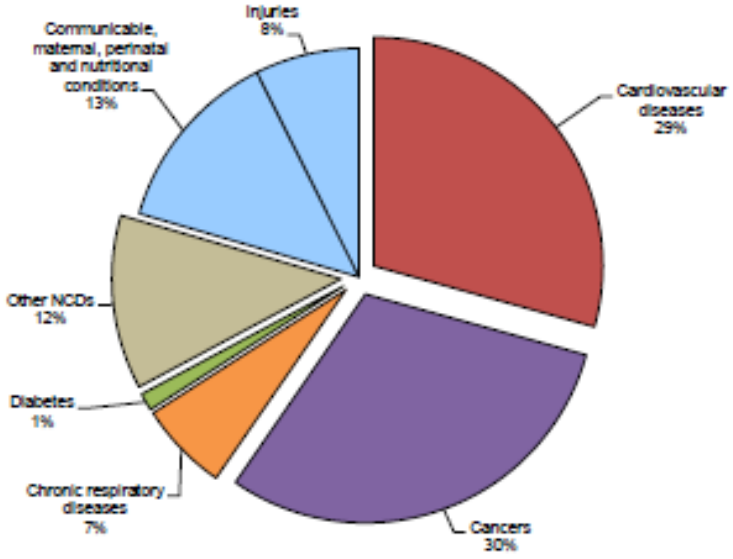
Realistic options
Germany or Japan

Japan vs Germany Demographics

	USA	Japan	Germany
Area ratio	100	4.0	3.8
Population ratio	100	40	25
Population growth rate	+0.78%	-0.16%	-0.17%
Seniors (65+)	15%	27%	21%
Birth rate (per 1k)	12.49	7.93	8.47
Death rate (per 1k)	8.15	9.51	11.42
Life expectancy	80 years	85 years	81 years
Fertility rate	1.87	1.40	1.44
GDP (PPP)	$ 17.4 T	$ 4.8 T	$ 3.7 T

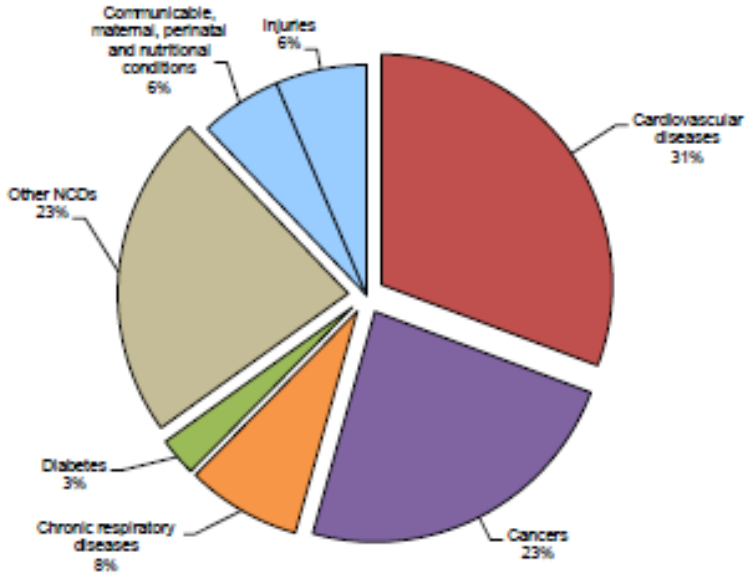
	USA	Japan	Germany
Health Expenditure (2012)	16.9% GDP	10.3% GDP	11.3% GDP
Public Expenditure on Health	47.6 %	82.1 %	76.7 %
Healthcare Out of Pocket	12.0 %	14.0 %	13.0 %
Physician Density (per 1k)	2.5	2.3	4.0
Nurse Density (per 1k)	11.1	10.5	11.3
Hospital Bed Density (per 1k)	2.9	13.7	8.3
Obesity	35.0 %	3.5 %	22.7 %
Hypertension	18.0 %	26.7 %	31.5 %
Tobacco smoker	14.0 %	21.0 %	22.0 %

Japan vs Germany
Causes of death



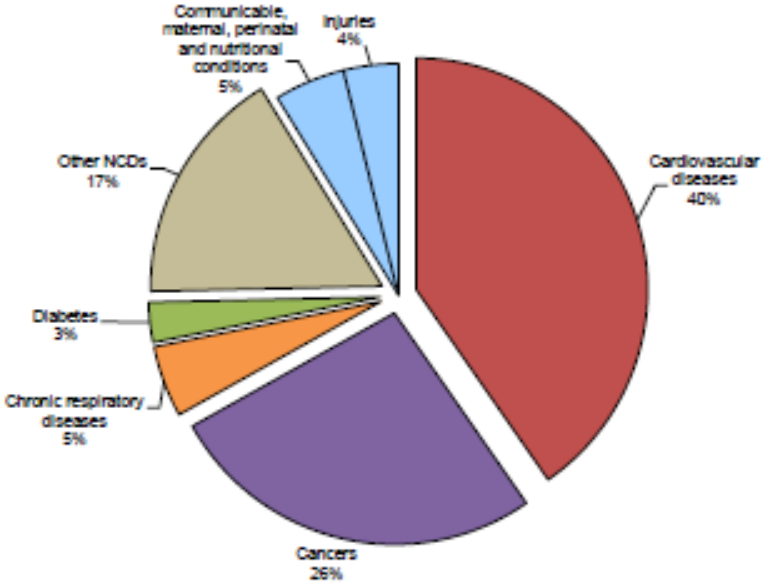
Total deaths: 1,192,000
NCDs are estimated to account for 79% of total deaths.

JAPAN



Total deaths: 2,656,000
NCDs are estimated to account for 88% of total deaths.

USA



Total deaths: 866,000
NCDs are estimated to account for 91% of total deaths.

GERMANY

Japan vs Germany Adult risk Factors

	Japan	USA	Germany
Obesity	3.5%	35.0%	22.7%
High BP	26.7%	18.0%	31.5%
Smoking	21%	14%	22%
Alcohol consumption	7.2 Liters	9.2 Liters	11.8 Liters

Japan in a snapshot

BASELINE POSITIVE

- No. 3 device market
- No.3 Healthcare spender
- HE is $332B and rising
- HE is 10.3% of GDP
- 40% of US population
- 27% is >65 years of age
- Universal Healthcare System
- Fair Valued Reimbursement
- Fast Adapter of New Technology
- Most westernized in Asia

RISKS & OPPORTUNITIES

- Heath Expenditure is twice of tax income
- 30% copay
- 22% tobacco smoker
- Obesity is only 3.5%
- Deaths are Cancer, Heart and Brain
- 10 M Hypertensive patients
- Bed Density is 13.7/1000
- Regulatory Complexity
- Language
- Risk Averse Society

Health Insurance System

- Universal Health Insurance System
- Uniform benefits and covers all eligible beneficiaries
- Ambulatory and hospital care, extended care, most dental care and Rx
- No HMO or PPO, can choose any hospitals or clinics
- Monthly premium based on annual income, little freedom to alter
- 30% copay for age 6 to 70, subsidized when spending exceed max per income
- No supplemental health insurance program
- Annual check up, birth, preventive medicine are not included

Reimbursement

- Reimbursement to healthcare providers are fixed by Chyuikyo
- Fee for service. DRG type pilot program in Public and Teaching Hospitals (routine)
- Medical service fee is not separated into Hospital and Physician fee
- Specific single use medical device (SIMD) are reimbursed separately
- SIMDs are 70 to 100% of US list price, diluted by EU and AZ list price
- Premium pricing for PMDA submission before or as same as FDA
- NHI does not pay anything if unapproved drug or device are used, all out of pocket
- Devices and non-routine procedures in regulatory clinical study not reimbursed
- Hospital charges x3 of NHI for workers compensation, accident injuries and so on.

Regulatory Landscape

- 3 path to commercialization: Registration, Certification and Approval
- Registration for Class I device
- Certification for Class II and III device with certification guidance
- Approval for Class II and III device w/o guidance, and Class IV
- Registration and Certification are granted to MAH (Market Release Authorization Holder)
- Approval is granted to MAH or Foreign Manufacturer with DMAH (Designated MAH)
- DMAH needs MAH license but does not need to own Product Approval
- DMAH can be changed by notifying MHLW
- Product Approval or Certification can be transferred if original holder agrees

Licenses and Registrations Needed

- MAH (Market release Authorization Holder) License
  - Responsible for the final market release of product
  - Product Shonin/Ninsho holder or in-country takecarer
- Manufacturing Registration
  - Design, main assembly, sterilization, storage (domestic)
  - Labeling can be done without registration if final release is done at domestic storage after labeling at registered site
- Sales and Rental - Needed at all sales offices to sell and store
  - Class III and IV - License
  - Class II – Register Class I – not necessary
- Repair – License
  - License per classification

PMDA scorecard

- ✓ PMDA review time is compatible to FDA for New Devices
- ✓ PMDA likes Foreign data + Japan data
- ✓ 50% of New Devices are approved with Foreign data only
- ✓ Apply Gap is huge, think about Japan from Day 1 and you will have a smooth ride
- ✓ Budget minimum of 3 years from application preparation to approval

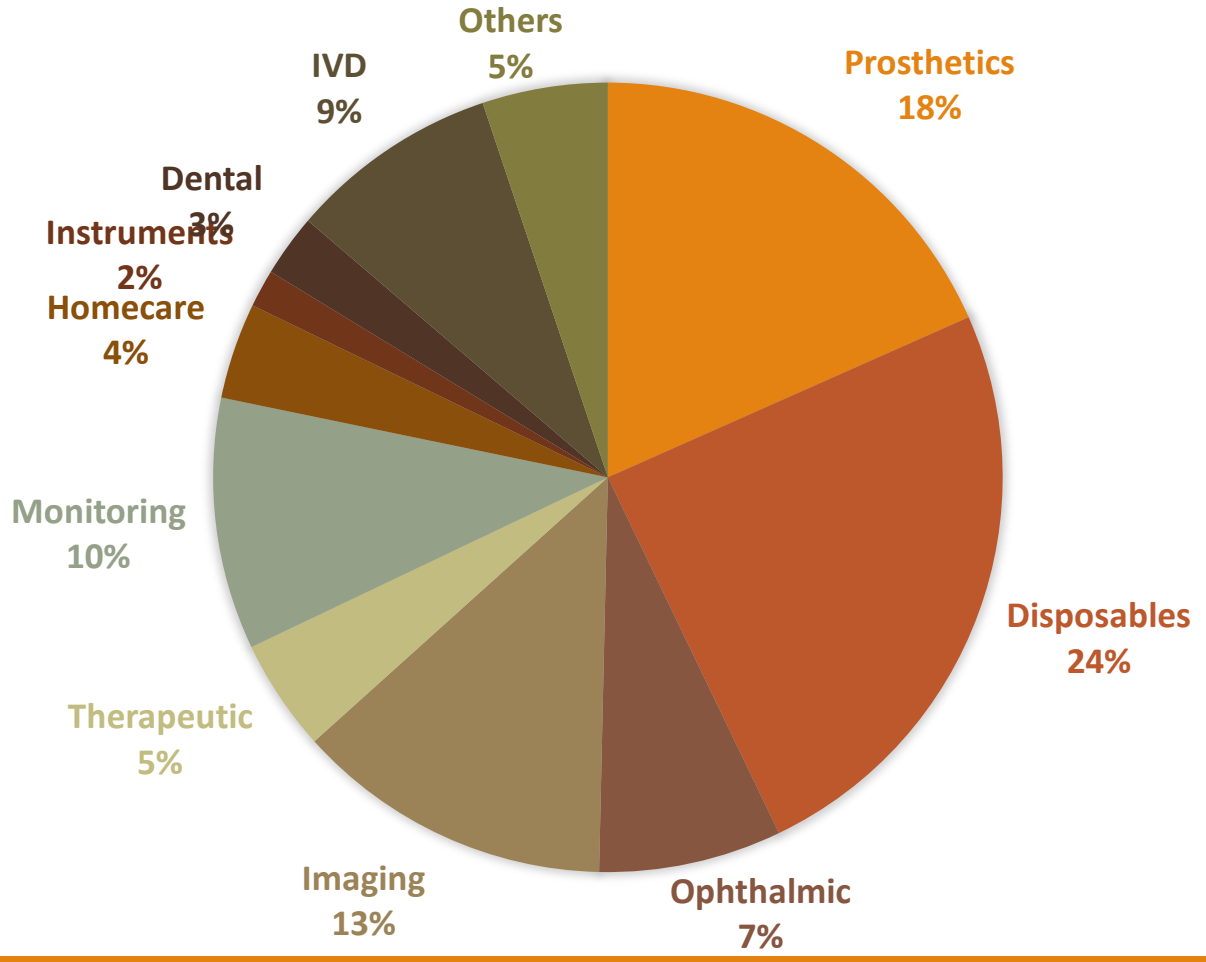
Government Programs

厚生労働省
Ministry of Health, Labour and Welfare

- **Unmet Clinical Needs (Device Lag)**
  - ✓ Petition by academic society or patient group
  - ✓ Severe disease, no or better alternative,
  - ✓ FDA cleared or CE marked, or great clinical data with no regulatory clearance
  - ✓ If designated, expedited review and reimbursement
- **Sakigake (Early Bird)**
  - ✓ Apply by industry
  - ✓ Innovative med tech, life threatening or presently no cure, highly effective and/or safe
  - ✓ Japan included in pivotal study
  - ✓ Japan first in term of regulatory submission
  - ✓ If designated, expedited review (2x) with PMDA coordinator and premium reimbursement
- **Senshin Iryo (Advanced Medicine)**
  - ✓ Apply by institution as clinical research
  - ✓ Unapproved or Unreimbursed procedure
  - ✓ Result can be used for regulatory approval
  - ✓ Result can lead to reimbursement
  - ✓ NHI covers standard of care fees
- **Patient Compassionate Use**
  - ✓ Apply by patient
  - ✓ Unapproved drug or device, no alternative
  - ✓ NHI covers standard of care fees
  - ✓ Only at Designated Hospital as clinical research

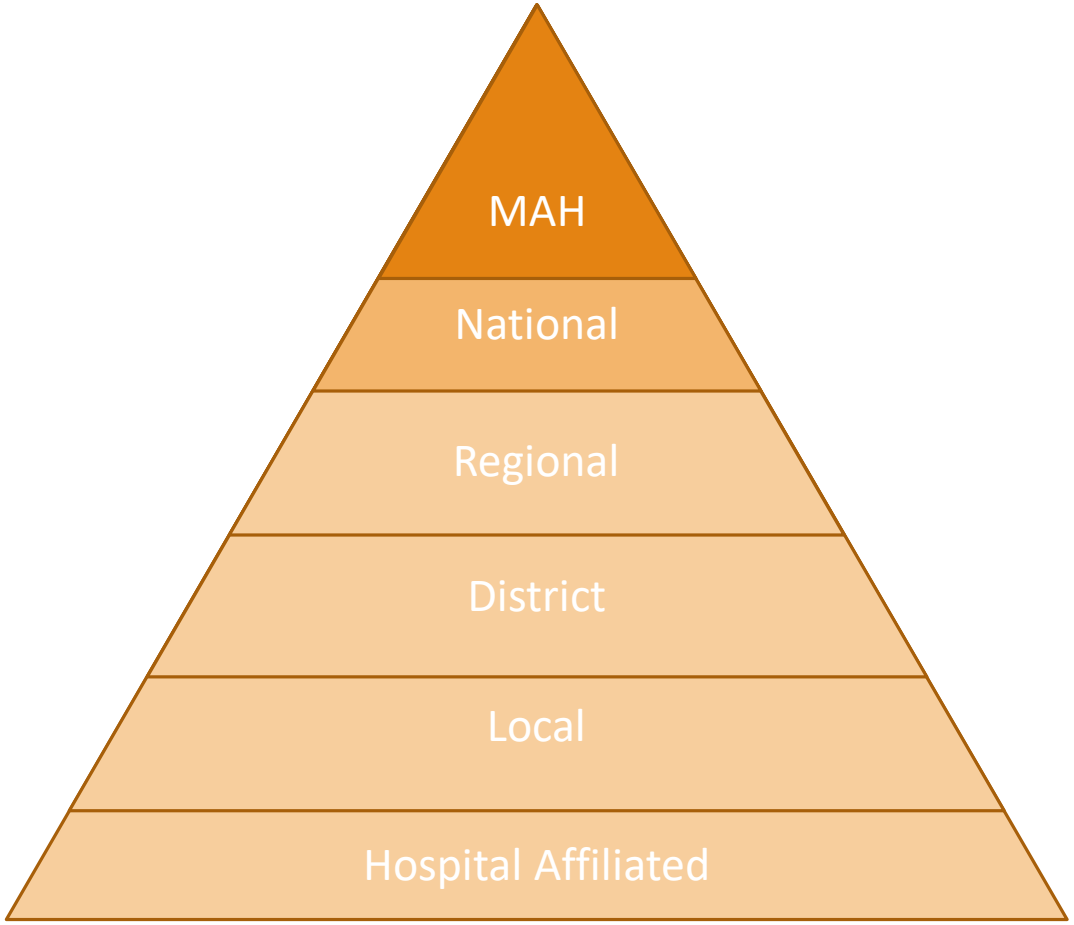
Medical Device Market Overview

- Third place ($30B) after US and China; followed by Germany
- 40% are imported, 50+% for high end diagnostic and therapeutic devices
- Once reimbursed, adoption rate of new medical technology is high
- 3 to 5+ years behind of US in term of new technology introduction
- Quality is No 1; local manufacturers' edge



Medical Device Market Distribution Channel

- Multi-layer, complex channel
- Limited accounts in hospital
- Hospital payment term is 6+ months
- Sales Activity is MAH/National driven
- Margin between 5 to 50%
- Purchase or Consignment
- Local distributor manages inventory
- Need distributor with account to negotiate price with hospital – anti-trust matter
- Product and documentation flow may not match



How to enter Japan?

1. Nationwide Distributor
2. Direct
3. Hybrid

Historical Approach: Low risk low return

1. Sign an agreement with a distributor, not really knowing the market
2. Give a copy of the regulatory dossier and have the distributor obtain the approval & reimbursement
3. Send same product as USA or EU
4. Visit once a year and complain that the numbers are not acceptable, with minimal support
5. Look for another distributor or consider going direct
6. Tough negotiation with approval holder on transfer of approvals
7. Go through couple GM to find the right guy or gal

Step 1:
Evaluate your business

- Does your product fill an unmet clinical need?
- Will your product be appropriately valued?
- Is the growth opportunity large?
- Is the projected ROI relatively large?
- Are you direct in USA?
- Is your product not capital intensive
- **Are you willing to invest as much as you did for the USA?**

Step 2: Reimbursement Decision Tree

Are comparable devices reimbursed?

YES
Additional Clinical Benefits?

NO
C2 Route

NO
A1/A2/B Route

YES
C1 Route

Heavy Activity
Need physician advocacy prior to **submission**

Minimal Activity
Register after approval

Moderate Activity
Need Physician advocacy prior to **approval**

Step 3:
Engage w/ Physician customers

- No user interest means no business
- Visit a broad user base and get direct feedback – the whole picture
- Get to know your customer first
- Are they willing to advocate for your technology?
- Are they wanting to use it before approval?
- Meet with them at conferences outside Japan – more time for you

Nationwide Distributor

PROS

- Low risk
- Small Investment
- Predictable early sales - inventory
- Earlier market entry
- Scapegoat selected
- Can always switch to direct if a homerun
- Quicker customer acceptance

CONS

- No or shallow control
- Filtered and biased customer voice
- One of many
- Sales focus on numbers, not your product
- Product clearance is hostage with ransom
- Possibly low margin
- Customer does not know you

Direct

PROS

- Full control
- Direct customer voice
- Focused ground troops
- New definition on quality
- building relations with stakeholders
- If done well, you will have your rewards

CONS

- Long term investment
- Trials and Errors, learning experience
- Japan will impact the whole company
- Patients is a virtue

Hybrid:
Maximize mutual benefits

- Own your product approvals
- Manage your products – MAH
- Have a transition plan to direct
- Consider Joint Venture
- Win-Win is key

Functions	Distributor	Direct
Sales	☐	☐
Marketing	☐	☐
Pre market regulatory	☐	☐
Post market regulatory	☐	☐
Reimbursement	☐	☐
Logistics/ Customer Service	☐	☐
Finance	☐	☐
General Administration	☐	☐

Your BUSINESS, BRAND, and PRODUCT

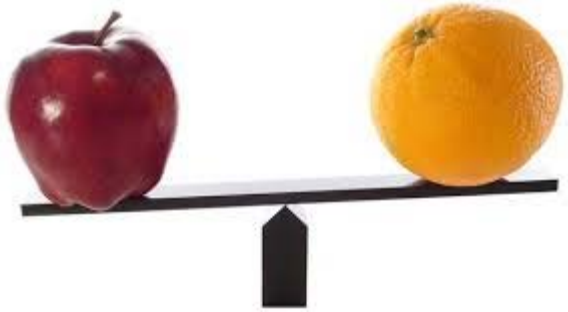
The key for success is fundamentally the same in Japan or US; It should operate based on:

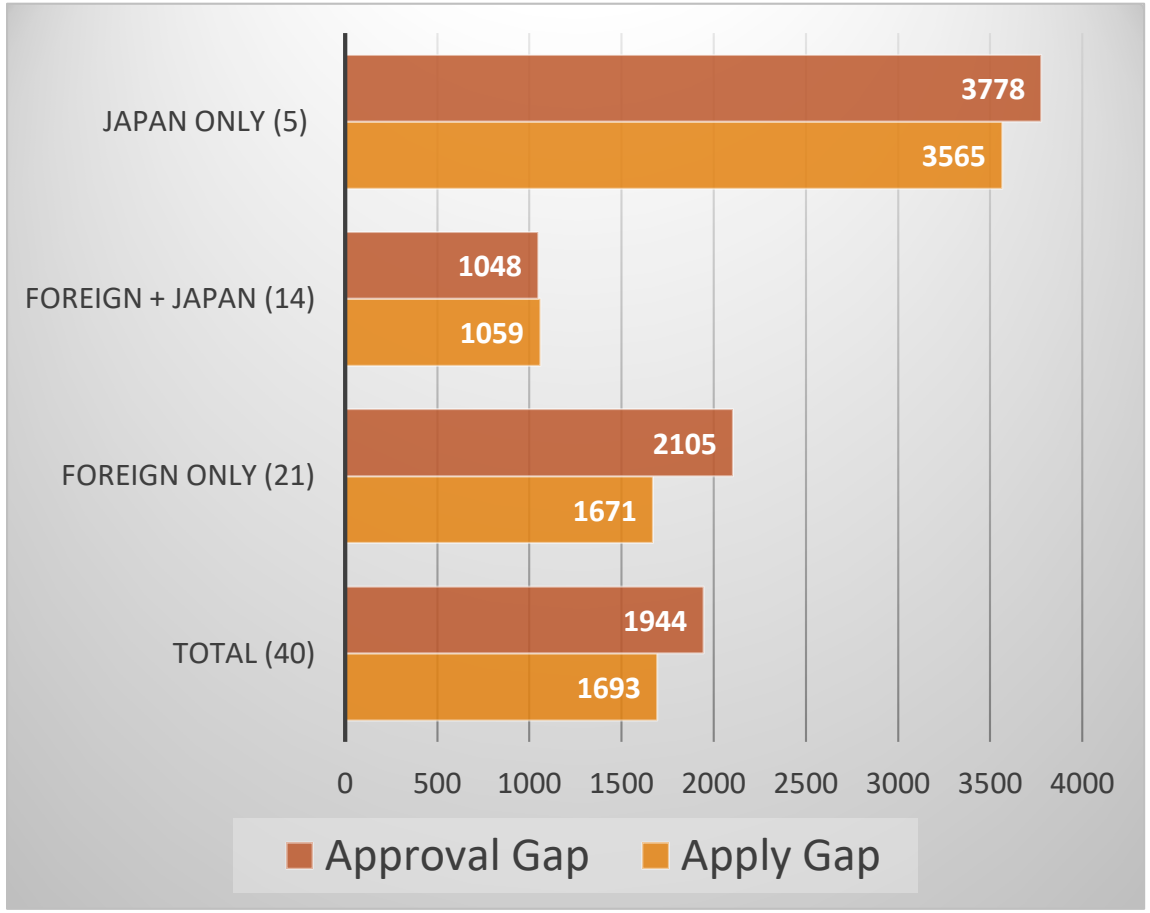
- Your corporate culture
- Your way of running business
- Your business objectives
- Your priorities
- Your thought processes
- With local favors

Facts about Japan

- Data shows no difference with Japanese manufacturer
- Reimbursement is 50% to 150% of Foreign Average Price
- US manufacturer can own the approval
- Japan **business** practice is basically the same from USA
- If you want 100% attention you have to go direct
- Physicians prefer using best devices for patient outcome
- Patients are more obedient to physician's recommendation

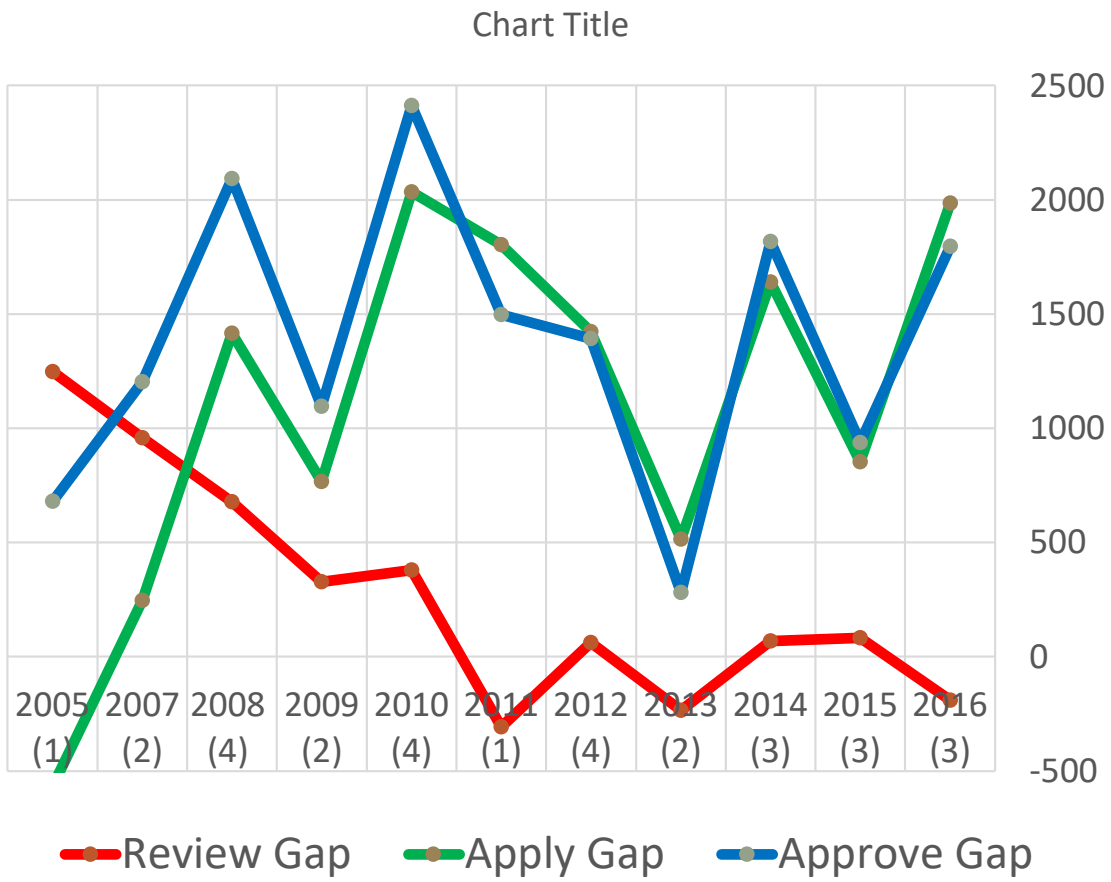
Is Japan Clincal Data Essential ?





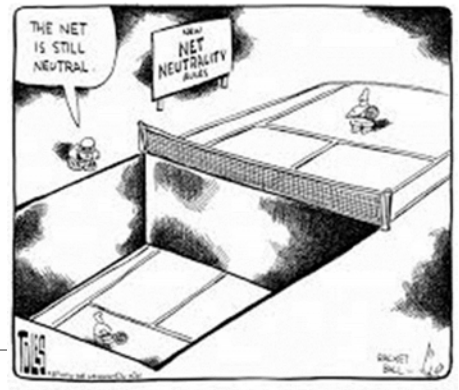
- Japan data only – rare cases
  - Device Generation Gap – old data?
  - GCP compliance?
- Extra Japan data is PMDA preference
  - Global study, Bridge study
  - Early consideration of Japan
- Foreign data only -
  - 50% of total New Device Submission
  - 50% are Urgent Clinical Need devices

Is PMDA slow?



- Review gap is the past!
  - There is practically no gap after 2011
  - PMDA is in range of FDA speed
  - 5 devices approved by PMDA earlier
  - 13 devices approved with shorter clock
- Apply gap has not changed
  - 1693 days behind FDA
  - Veterans (33) are 1563 days behind FDA
- Approval gap is in line with review gap

PMA versus 510k Days to approval



PMDA Track	FDA Track	n	PMDA Review	FDA Review	*p* value
Novel	PMA	16	520	535	*ns*
	PMA Supp	6	354	349	*ns*
	510k	18	661	277	*<0.05*
	HDE	3	766	430	*ns*
Improved	PMA	26	646	522	*ns*
	PMA Supp	19	473	209	*<0.05*
	510k	77	617	138	*<0.05*

How different is Japan, really? My view

- 80% are fundamentally the same
  - Same but different depths
  - Customers' expectation
- 20% are different
  - Risk averse culture
  - Socialized government
  - Hunting versus Farming Society
- Inflation of the 20% differences
  - Preference, Practice or Perception
  - Who is inflating? Whose excuse?

The Devils in the details! Audit your dossier

- Medical Device Essential Principle Checklist: TGA format is similar
- ISO14971 Risk Management: for Japan
  - population, practices, expectation
- MDRs: Proof of Design Review and Risk Management
- Accelerate versus Real-time Aging
- Test samples: rationales and/or justifications
- Biocompatibility: fine prints in ISO10993
- Intended Use: Evidence Based
- Voltage: Japan is 100V 50/60 Hz
- Residual ETO gas
- Quality of Translation, Emendation,
- DVV Test reports: Pristine? Traceability?
- Specifications: rationales and/or justifications
  - Dimension linked to safety and effectiveness
  - Tolerances
- Consistency in nomenclature
- WHY is missing: selection, acceptance criteria
- Signed off with lots of mistakes or incorrect information
- 510k approach is not accepted
  - A+B does not equal C, it is only A+B
- Screening, processing, inspection and traceability of biologics
- Raw material listing
- Tables, Graphs preferred rather than narrative

25 years of Lesson Learned (1)

- Go with the first distributor knocking on the door
- Agree on pricing not knowing local reimbursement price
- Clinical use at only one hospital with physician license importation
- Believe the distributor about regulations
- Agreement guarantees transfer of approval
- FDA approval is paramount
- Good clinical outcome means GCP complied study
- Published clinical data in peer reviewed journal means GCP complied study
- PMDA will not read every single attachment
- Establish local entity early and hope for the best; local knows the best
- Opportunity will come again
- Japan will listen to the States
- Bureaucrats will bow to politicians without any retaliations
- Reporting to government is to inform and not to fully closure
- Suspension of business by MHLW is a temporary matter
- Hire a GM then all is done, your headache is gone and you will be successful

25 years of Lesson Learned (2)

- Japan is different is the best excuse; tell me more about it
- We should not negotiate or discuss with the government, just follow their rules
- It has been done this way so we should not challenge it; do not rock the boat
- Seniority may be stronger than title; be aware
- “Hai” is only an acknowledgement
- It is easy to hire people; wrong!
- Career advancement only by hopping jobs is not a good sign
- Be aware of those who only hire non-English speaking staffs; job security
- Why do people want to switch job? Best are those who do not want to
- Look outside the industry for talents
- Get to know him or her; have them work in the States, mold them to your culture before you hand on the GM role
- Medical professionals working in the industry are losers from the eye of the customer; have them keep the clinical practices
- Succession planning is paramount
- Subsidiary long in Japan is more Japanese than domestic companies
- Buying your distributor is more buying their culture than the distribution; be aware

When to think about Japan Hindsight is 20/20

Situation	Risk	Extra investment or lost of opportunities	Time to market lag
• After successful EU & US launch • Not prepared for Japan	• Original staff are gone • Test reports are not sufficient • Studies are not GCP compliant • Product generation gap • Can not build legacy product • Unfavorable Reimbursement	$$$	Min 3 to 5 Years
• After successful EU & US launch • Prepared for Japan	• Original staff are gone • Test reports are sufficient • Key Studies are GCP compliant • Product generation gap • Need to build legacy product • Acceptable Reimbursement	$$	Min 1.5 to 3 Years
• Japan as Priority No 1 International market	• Original staff are still in-house • Test reports are sufficient • Key Studies are GCP compliant • Acceptable Reimbursement	$	Min 6 to 18 Months

Key Takeaway
JAPAN NOW

- Japan is worth your time & money, if you do right
- Meet Japanese customers; listen and learn
- Consider Direct, Distributor and Hybrid
- Reimbursement is key
- if 510k cleared, upgrade is essential
- Stand firm on your vision, cultures and objectives

Satisfy your most demanding customer then the rest of the world will love you

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