Premarket Registration Requirements in Multiple Markets across Korea, Japan, China, US, and EU

Kyungyoon Kang, Regulatory Affairs Manager, MSA, RAC
St. Jude Medical USA

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1-A: GLOBAL MEDICAL DEVICE MARKET OVERVIEW

- The US medical device market is the world's largest with $125.4bn, followed by Europe and Asia with $95bn and $60bn respectively in 2013.

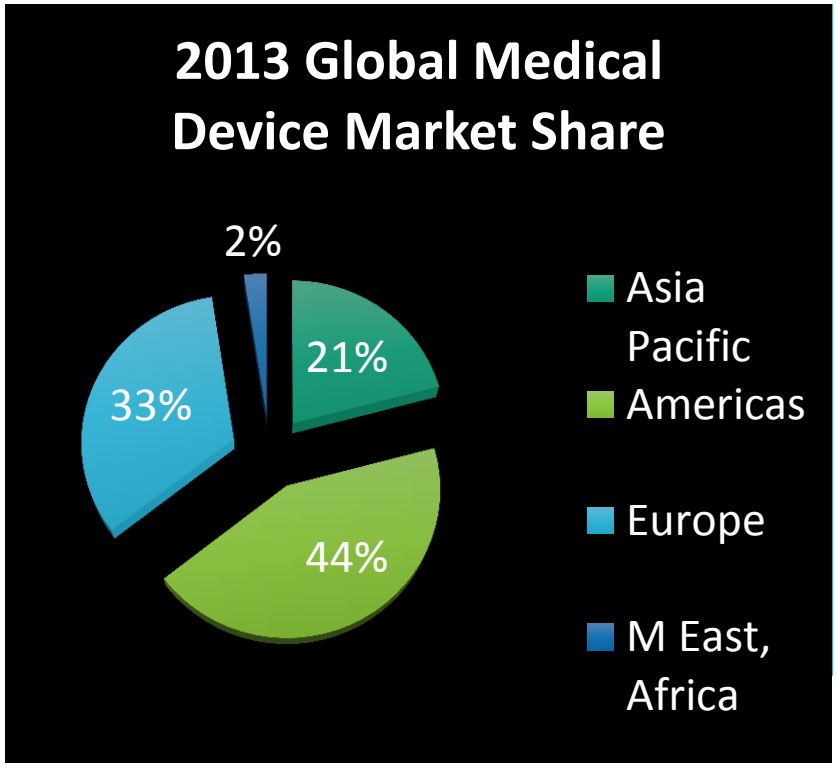

Table 1-A-1 Global Medical Device Market Share

- Asia's emerging markets' healthcare expenditures are projected to grow 2-3 times faster than the global average.

Table 1-A-2 Global Healthcare Expenditure Forecast

Source: *BMI, Bain Analysis*

1-B: Global MEDICAL DEVICE MARKET GROWTH

The global medical device market is projected to grow by 4.4% per year to reach $440bn in 2018.

- Medical device market with 4.4% annual growth is set to outperform the prescription drug market of 2.5% growth per year between 2011 and 2018.
- The fastest growing segment within top 15 is neurology, which is set to grow at 6.1% annually till 2018.

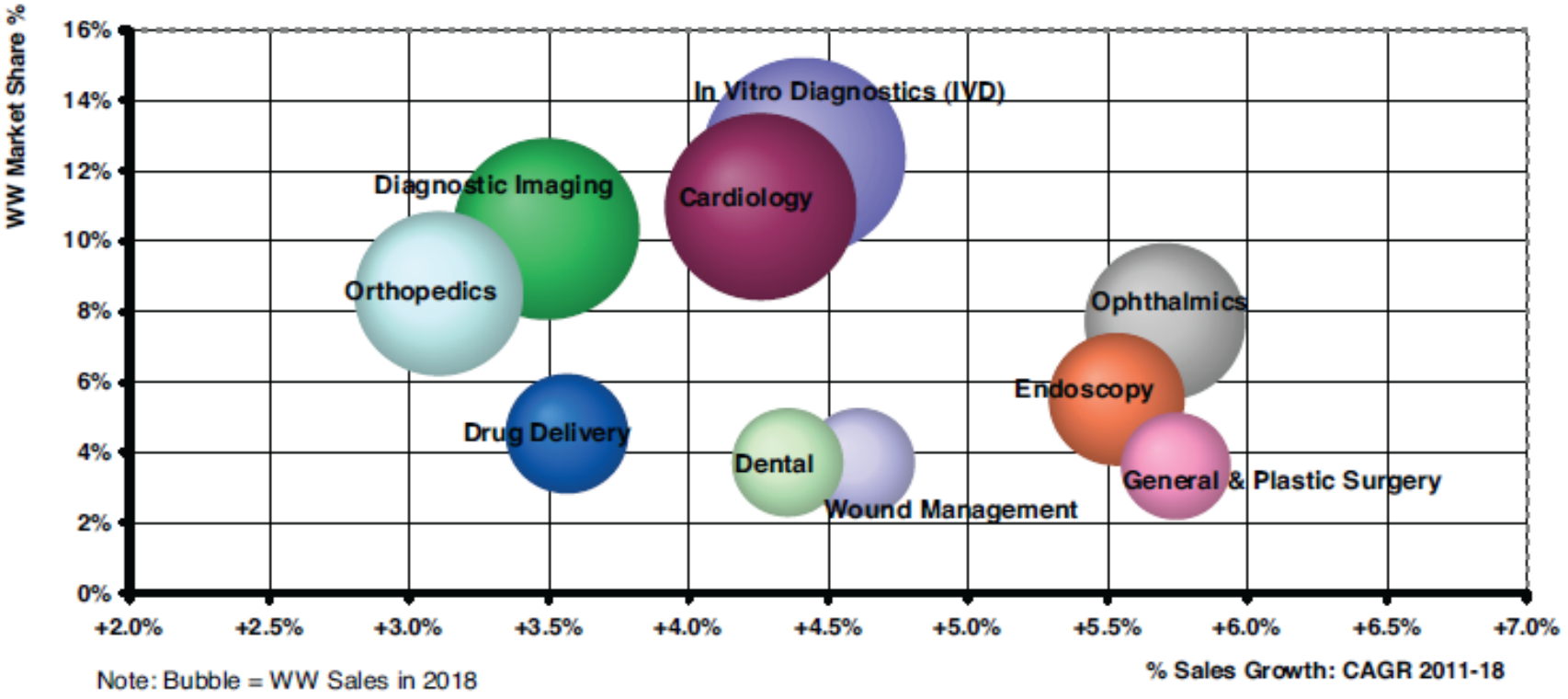

Figure 1-2. Top 10 Medical Device Areas- Worldwide Market Share (Projected 2018) and Sales Growth Rate (2011-2018)

Source: *Evaluate MedTech-WorldPreview 2018*

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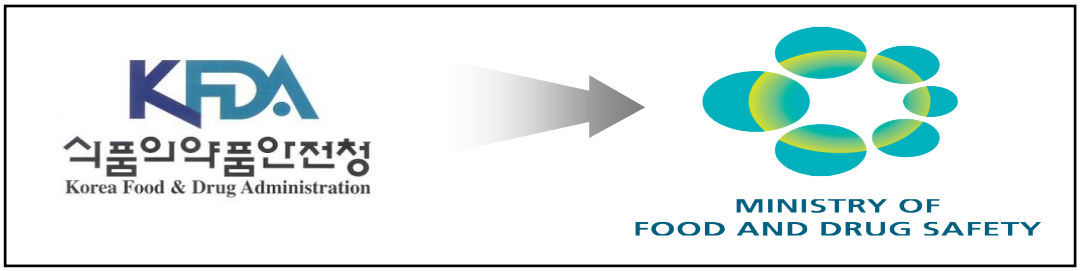
2-A: KOREA MINISTRY OF FOOD AND DRUG SAFETY

In March 2013, formerly the Korea Food and Drug Administration changed its name to Ministry of Food and Drug Safety with an update in statutory authority.

2013 Changes

- Set up "control tower" to bolster the food safety management system
- Regulator's allocation of administrative duties at the departmental level
- Policy making and development function remains within the Headquarters while the duties relating to enforcement, monitoring, and evaluation are transferred to the Regional Food and Drug Administration.



2014 Changes

- Beginning in January 2014, Submissions for Class IV devices (equivalent to US FDA class III devices) are required to be made on the STED basis, while lower class device applications may be submitted either through the STED or conventional application format.

Source: Ministry of Food and Drug Safety

2-B: DEVICE PRODUCT FAMILY for KOREA/JAPAN

Medical Device Classification: Risk-Based Regulation

- Based on harmonization efforts with GHTF/IMDRF, 4 classes are built given potential risks to human health and purpose of use. 2,206 items are designated by Ministry Notification in Korea, whereas 4,044 JMDN codes are established for Japan.

- It is important to set-up device classification strategy appropriate for Asia including Korea, Japan (JMDN), China and other AHWP member countries (broadly following GMDN) .

Device Classification	Regulatory Path	Review Party	Number of Classified Devices
Class I	Minimal Risk	Forceps for Medical Use	601
Class II	Low Risk	Syringe, infusion pump	1008
Class III	Moderate Risk	Contact lens	254
Class IV	High Risk	Coronary stent, PTA Balloon Catheter (Class II => IV)	341

Table 2-B Medical Device Risk Classification-Korea

Source: *Korea Ministry of Food & Drug Safety, Fundamentals of Japanese Regulatory Affairs,* RAPS

2-C: COMPARISON OF KOREA & JAPAN REGULATORY REQUIREMENTS

Premarket Registration Pathway & Requirements

Device Classification		Regulatory Path		Review Party			Requirement	
Korea	**Japan**	**Korea**	**Japan**	**Korea**		**Japan**	**Korea**	**Japan**
Class I	General Medical Devices	Notification	Self-Certification	MFDS: 0 months		PMDA: 0 months	Device Description: Non-Approval Process	
Class II	Controlled Medical Devices	Technical Document Review	Nin-Sho Certification: Products Compliant with Certification Standards	- SE/Modified Devices: MFDS Authorized 3rd Party Institute: 25 Days	Approval-MFDS Regional Office: 10 Days	Recognized Certification Body: 3-6 Months	- Recognized SE Device: Test Report for Safety & Performance - SE/Modified Device: Test Report for Safety & Performance, Comparison Data	Recognized certification body assesses conformity to the certification standards and QMS. The certification standards comprise the nomenclature and JIS as technical standards.
Class III Class IV	Specifically Controlled Medical Devices	Technical Document Review STED Format Submission	Shonin Approval from MHLW	- New : MFDS Medical Device Evaluation Dept: 55 Days - Medical Device Evaluation Dept: 70 Days - Clinical Study Plan Approval: 30 Days	Approval-MFDS Headquarter: 10 Days	PMDA: 8-16 months	New Device: Aforementioned data + Additional Safety, Performance Data, Origin, Development Process, Clinical Data, Overseas Usage Status	Submit application documents to prove that device safety and effectiveness have been demonstrated per Article 40, Paragraph 1 of PAL, Enforcement Regulations

Source: *Korea Ministry of Food & Drug Safety, Fundamentals of Japanese Regulatory Affairs,* RAPS

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3-A: US FDA/EU Notified Body Regulatory Strategy

1. Set up primary registration direction and target.

Start with clear RA directions and targets.

1) Device Generation 1
US
- Target Submission: Aug 2015
- Submission pathway: PMA Supplement
- Target Approval: Q1 2016

Europe (CE Mark)
- Target Submission: Aug 2015
- Submission pathway: Design dossier
- Target Approval: Q4 2015

2) Device Generation 2
(Significant Modification to Gen 1)
US
- Target submission: Q2 2016 upon IDE completion
- Submission pathway: PMA supplement

Europe (CE Mark)
- Target submission: Q2 2016
- Pathway: Design dossier
- Target approval: Q3 2016

2. Confirm registration platform with FDA & EU NB.

Align RA strategy with agency guidance.

1) Gen 1 Pre-submission meeting
- FDA : June 2015 (Question submission, Sept 2015 (Meeting) (Discuss modified design)

2) Gen 2
- FDA: Schedule Pre-submission meeting prior to IDE
- EU Notified Body: Pre-submission meeting: Review of CER (literature data)

3. Anticipate and prepare for FDA & EU NB hurdles.

Be prepared.

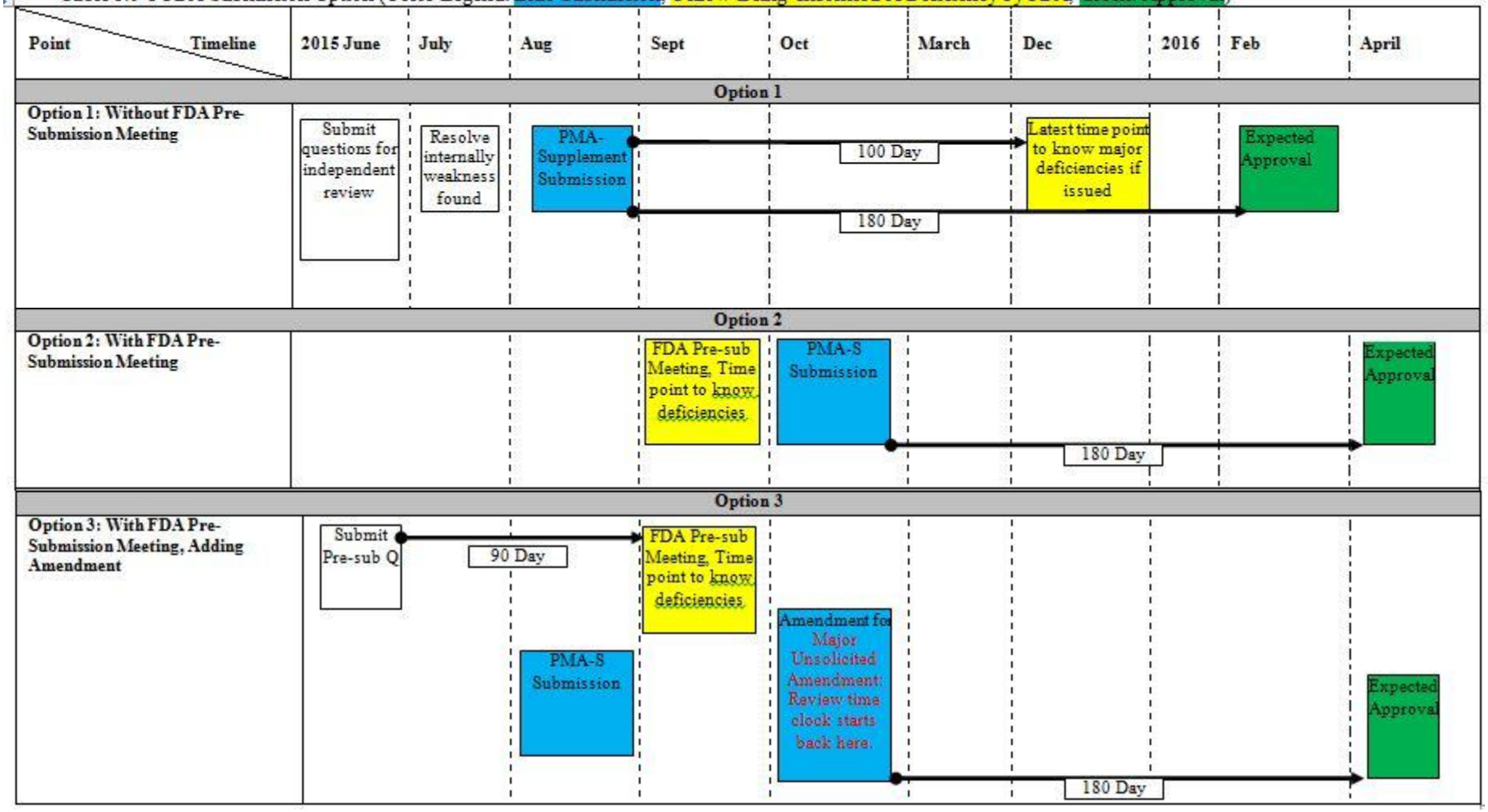
1) FDA
Non-clinical: Evaluate the biocompatibility risk assessment (FDA's G95-1 vs ISO 10993, colorants)
Pre-clinical: Animal study
Clinical: Clinical requirements aligned through pre-submission meeting

2) EU Notified Body
Obtain concurrence on the pre-market (V&V, animal study) data and post-market study proposal.

The aforementioned information is written based on hypothetical scenarios of pre-market registrations.

3-B: US FDA Regulatory Strategy

Table 1.0-1 FDA Submission Option (Color Legend: Blue-Submission, Yellow-Being Informed of Deficiency by FDA, Green: Approval)



The aforementioned information is written based on hypothetical scenarios of pre-market registrations.

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4-A RAW MATERIAL REQUIREMENT-JAPAN

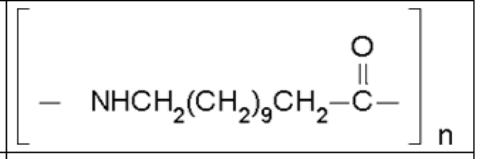
Preparing Spec 19 tables for patient-contacting materials may require extensive time resources to gather the raw material information.

STED Section 3

No	Component	Raw Material Name	Specification Table	Contact blood, tissue, or body fluid?
5 Fr. Central Venous Catheter				
1	Extension Tube	Polyamide resin (nylon xx)	Note 1	Yes
2	Winged Hub	Polyethylene	Note 2	Yes
3	Extension Hub	Nylon Polyamide 12	Note 3	Yes
4	Catheter Shaft	Polyurethane	Note 4	Yes
5	Markings	Ink # 1234	Note 5	Yes
6	Adhesive	Cyanoacrylate	-	No
7	Coating	Rifampin	Note 6	Yes

SPEC 19 Table

Note 1: Polyamide resin (nylon XX)

Standard item			
A. Generic name or common name	Polyamide resin (nylon XX)		
B. General chemical information			
1. Chemical name	Polyimino(1-oxo-1, 12-dodecanediyl)		
2. CAS registry number, USAN, and registration number under the Law Concerning Examination and Regulation of Manufacture, Etc. of Chemical Substances	CAS registry number: 12345-67-8		
3. Structural formula			
4. Molecular weight, etc.			
C. Information from the raw material manufacturer, etc.			
1. Name of manufacturer	Raw Material Inc.		
2. Product name (or brand name)	Raw Material Inc. 56789		
3. Manufacturing number or code	RMI Compound 56789—Dark Blue		
4. Raw material standard and product specifications			
5. Types and volumes of additives	Additive	CAS #	Percent by weight
	CI Pigment Black 1	1234-56-7	2.0%
	CI Pigment Blue 2	123-45-6	1.0%
	CI Pigment Green 3	1234-12-3	1.0%
	Zinc Stearate 5	123-45-6	<1.5%
D. Official standard name and number			
1. JIS, ISO, and ASTM medical device material standard			
2. JP, USP, and EP medical device or pharmaceutical standards			
3. Other official standards			
E. Master file registration number			
F. Chemical analysis			
1. Identification and assay of organic solvent extracts, etc.			
2. Material chemical test			
3. Polymer structure analysis			

Avoid making any errors for contacting material information in STED Section 3-Spec 19 table

Note: Aforementioned raw material data are not the real device information.

4-B RAW MATERIAL REQUIREMENT-GLOBAL COMPARISON

Japan, Korea, China, and United States:

- Understanding raw material data requirements from a global scope helps establish a streamlined process to gather required information that comprehensively meets regulatory requirements of target regions.

Agency	Japan-PMDA	Korea-MFDS	China-CFDA	US FDA
Chemical Name	Required for all			
Standard	ISO, ASTM, USP			Not required
	JIS, JP	KS, KP accepted, CAS # is no longer accepted as a material standard.	CAS # can be provided.	CAS # can be provided in lieu of standards.
% of ingredients by weight	**Submit if no standards are obtained.**	**Submit if no standards are obtained.**	Submit if no standards are obtained.	Possibly be asked through 510k, PMA inquiries for colorants
Specification	Density, specific gravity, tensile strength, melting point, PH, Hardness, Appearance	List the manufacturer/vendor's own specification such as viscosity, density, dissolution range, strength. Specification can be derived from what's listed on the Certificate of Analysis. MSDS is required.	Material specifications	Not required if CAS numbers are provided.

4-C BUILDING INTERNAL CONTROL THAT MEETS GLOBAL REGULATORY REQUIREMENTS FOR RAW MATERIALS

- Establishing internal control on material data is a key to keep up-to-date registration information with the MFDS, PMDA, CFDA, US FDA, and EU Notified Body.

1. Building internal control on raw material data

1) Establishing the control system for material data required by regulatory agencies would alleviate immense regulatory workloads of retroactively checking data.

2. Mitigating business risks with vendors

1) Vendors may be reluctant to agreeing to impose control of material data.

2) QA/Purchasing Inquire vendors as to what types of material data are considered as specifications or information traceable.

3. Building control system reflecting both regulatory & business needs

1) For submissions, Regulatory uses only data identified as controlled or traceable by vendors.

2) QA/Purchasing require vendors to sign a letter stating, “vendor XXX agrees to notify company XXX of material or process changes that could affect the safety, performance of the product.”

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5-A COMPARISON OF APAC BIOCOMPATIBILITY STANDARDS WITH US FDA GUIDANCE & ISO 10993

Initial Evaluation Tests for Consideration													
Categorization			Biological Effect										
Nature of Body Contact		Contact duration A- Limited (<24h) B- Prolonged(24h to 30 days) C- Permanent (>30)	Cytotoxicity	Sensitization	Irritation or Intracutaneous Reactivity	(acute)Systemic toxicity	Pyrogenicity	Subacute andsubchronic toxicity	Genotoxicity	Implantation	Hamocompatibility	Chronic Toxicity	Carcinogenicity
Category	Contact												
Surface Device	Skin	A	X	X	X								
		B	X	X	X								
		C	X	X	X								
	Mucosal Membrane	A	X	X	X								
		B	X	X	X	O		O		O			
		C	X	X	X	O		X	X	O			
	Breached or Compromised surface	A	X	X	X	O	△						
		B	X	X	X	O	X	O		O			
		C	X	X	X	O	X	X	X	O		△	
External communicating device	Blood path, indirect	A	X	X	X	X	X				X		
		B	X	X	X	X	X	O			X		
		C	X	X	O	X	X	X	X	O	X	△	
	Tissue/bone/dentin	A	X	X	X	O	△						
		B	X	X	X	X	△	X	X	X			
		C	X	X	X	X	△	X	X	X		X	X
	Circulating blood	A	X	X	X	X	X		O		X		
		B	X	X	X	X	X	X	X	X	X		
		C	X	X	X	X	X	X	X	X	X	X	X
Implant device	Tissue, bone	A	X	X	X	O	△						
		B	X	X	X	X	△	X	X	X			
		C	X	X	X	X	△	X	X	X		X	X
	Blood	A	X	X	X	X	X	X		X	X		
		B	X	X	X	X	X	X	X	X	X		
		C	X	X	X	X	X	X	X	X	X	X	X

(X

Source: ISO 10993-1, 2003, Japan MHLW Yaku 0301, US FDA G95-1 Memorandum, 2013 Korea MFDS Biological Safety Standard, **China**: GB/T 16886.1

5-B UNDERSTANDING BIOCOMPATIBILITY REQUIREMENTS FROM GLOBAL STANDPOINT

- Facilitating biocompatibility test arrangements needs to be done under a comprehensive biocompatibility risk assessment plan that meets the requirements of major target regions.

Biocompatibility Requirement	Japan MHLW	Korea MFDS	China CFDA	US FDA
GLP Test Report	Generally Required	Strictly Required	Generally Required	Recommended
Finished Device Test: Test article same as proposed device	Recommended, but leveraged testing performed on raw materials as the same as those of the predicate devices can be accepted.	Required	Recommended	Recommended, chemical characterizations of colorants can possibly be asked through 510k, PMA inquiries.
Test sponsor same as the proposed device manufacturer	N/A	Required	N/A	N/A
Time points of Test report issuances	For Ninsho submissions, if test reports were issued prior to the year of the latest amendment of ISO 10993-1, justifications need to be provided.	MFDS only accepts test reports that have been issued within the last three years. Otherwise, provide a justification in the notarized certification format.	If test reports were issued prior to 2003, ISO 10993-1 (2003), justifications may need to be provided.	N/A
Notable differences with ISO 10993 (2009)	N/A	MFDS Standards recommend additional test considerations. (Pyrogenicity, Genotoxicity test for externally communicating devices with short-term blood contacts)	CFDA biocompatibility standards correlate to the prior 2003 version of ISO 10993-1. (Hemocompatibility-short term: Blood coagulation/PTT)	FDA G95-1 guidance recommends additional test considerations. (Genotoxicity, In-vivo testing, Hemocompatibility: Complement System, Pyrogenicity)

Source:

Japan: Yaku 0301 Concepts for Evaluation of Biological Safety

Korea: MFDS Common standard for Biocompatibility Safety of Medical Devices (04-05-2013)

China: GB/T 16886.1

US: FDA Draft Guidance for Industry and FDA Staff: Use of ISO 10993 (04-23-2013)

5-C APAC NON-CLINICAL TESTING STRATEGY

- APAC-wide testing gap assessment enhances registration process-efficiency of ensuring appropriate verification/bench testing arrangement for the APAC region.

APAC Business Unit 1		Not indicated To be Registered	Test Gap Assessments for Priority Registration Item			Currently Available Performance Test Report
Non-Clinical Test Assessment		To be registered				
11/17/2014		APAC Assessment				
Priority #	**Device Name**	**Korea**	**Japan**	**China**	**APAC Assessment**	
1	ABC Stents	Registration file complete except Performance testing (aging) needed.	1 No JIS available, Please Proceed with ISO	Shelf Life testing ongoing	Korea and Japan would use testing arranged for China. Biocompatibility testing needed	Bend Testing
2	DEF Stent Sets	Registration file complete except testing section		1 Under CFDA Review	Shelf life, biocompatibility test need to be arranged for Korea and Japan	Tensile Testing
3	DDD Needle		4 Enginnering performance test gap analysis	Renewal, Shelf life testing completed. local China testing ongoing	N/A	Not available
4	EEE Wire guide	Approved with MFDS	JIS Provided to Engineering	Wire to be registered	Need to consider using testing used for Korea registration	Tensile Test Corrosion Test
5	K Dilator Set	Registration file complete except testing section	No JIS Available, Proceed with ISO	New Registration, Shelf life testing has been requested.	Korea and Japan would use shelf life testing requested for China.	Not available

Note: Aforementioned data does not represent the real device information.

QUESTIONS?

KYUNGYOON KANG, MSA, RAC
Regulatory Affairs Manager
St. Jude Medical
Phone: 1 972-309-2173
Email: kkang02@sjm.com