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

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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.

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

Table 1-A-1 Global Medical Device Market Share

Table 1-A-2 Global Healthcare Expenditure Forecast

Source: BMI, Bain Analysis
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
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).

<table>
<thead>
<tr>
<th>Device Classification</th>
<th>Regulatory Path</th>
<th>Review Party</th>
<th>Number of Classified Devices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Minimal Risk</td>
<td>Forceps for Medical Use</td>
<td>601</td>
</tr>
<tr>
<td>Class II</td>
<td>Low Risk</td>
<td>Syringe, infusion pump</td>
<td>1008</td>
</tr>
<tr>
<td>Class III</td>
<td>Moderate Risk</td>
<td>Contact lens</td>
<td>254</td>
</tr>
<tr>
<td>Class IV</td>
<td>High Risk</td>
<td>Coronary stent, PTA Balloon Catheter (Class II =&gt; IV)</td>
<td>341</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Device Classification</th>
<th>Regulatory Path</th>
<th>Review Party</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I</strong> General Medical Devices</td>
<td>Notification</td>
<td>Self-Certification</td>
<td>MFDS: 0 months</td>
</tr>
<tr>
<td><strong>Class IV</strong> Specifically Controlled Medical Devices</td>
<td>STED Format Submission</td>
<td>Approval-MFDS Headquarter: 10 Days</td>
<td>Source: Korea Ministry of Food &amp; Drug Safety, Fundamentals of Japanese Regulatory Affairs, RAPS</td>
</tr>
</tbody>
</table>

Submit application documents to prove that device safety and effectiveness have been demonstrated per Article 40, Paragraph 1 of PAL, Enforcement Regulations.
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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.
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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

<table>
<thead>
<tr>
<th>No</th>
<th>Component</th>
<th>Raw Material Name</th>
<th>Specification Table</th>
<th>Contact blood, tissue, or body fluid?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Extension Tube</td>
<td>Polyamide resin (nylon xx)</td>
<td>Note 1</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Winged Hub</td>
<td>Polyethylene</td>
<td>Note 2</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>Extension Hub</td>
<td>Nylon Polyamide 12</td>
<td>Note 3</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Catheter Shaft</td>
<td>Polyurethane</td>
<td>Note 4</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Markings</td>
<td>Ink # 1234</td>
<td>Note 5</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>Adhesive</td>
<td>Cyanoacrylate</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>Coating</td>
<td>Rifampin</td>
<td>Note 6</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Agency</th>
<th>Japan-PMDA</th>
<th>Korea-MFDS</th>
<th>China-CFDA</th>
<th>US FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemical Name</strong></td>
<td>Required for all</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Standard</strong></td>
<td>ISO, ASTM, USP</td>
<td>KS, KP accepted, CAS # is no longer accepted as a material standard.</td>
<td>CAS # can be provided.</td>
<td>CAS # can be provided in lieu of standards.</td>
</tr>
<tr>
<td><strong>% of ingredients by weight</strong></td>
<td>Submit if no standards are obtained.</td>
<td>Submit if no standards are obtained.</td>
<td>Submit if no standards are obtained.</td>
<td>Possibly be asked through 510k, PMA inquiries for colorants</td>
</tr>
<tr>
<td><strong>Specification</strong></td>
<td>Density, specific gravity, tensile strength, melting point, PH, Hardness, Appearance</td>
<td>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.</td>
<td>Material specifications</td>
<td>Not required if CAS numbers are provided.</td>
</tr>
</tbody>
</table>
Overcoming Challenges for Data Control

What challenges does Cook need to overcome in order to implement the material data control?

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.”

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.
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## 5-A Comparison of APAC Biocompatibility Standards with US FDA Guidance & ISO 10993

### Initial Evaluation Tests for Consideration

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Category</td>
<td>Contact</td>
<td>Contact duration</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(&lt;24h)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(24h to 30 days)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(&gt;30)</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucosal Membrane</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breached or Compromised surface</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood path, indirect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>External communicating device</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue/bone/dentin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circulating blood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implant device</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table:

<table>
<thead>
<tr>
<th>Nature of Body Contact</th>
<th>Biological Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cytotoxicity</td>
</tr>
<tr>
<td>Skin</td>
<td>A X X X</td>
</tr>
<tr>
<td>Mucosal Membrane</td>
<td>A X X X</td>
</tr>
<tr>
<td>Breached or Compromised surface</td>
<td>A X X X</td>
</tr>
<tr>
<td>Blood path, indirect</td>
<td>A X X X</td>
</tr>
<tr>
<td>External communicating device</td>
<td>A X X X</td>
</tr>
<tr>
<td>Tissue/bone/dentin</td>
<td>A X X X</td>
</tr>
<tr>
<td>Circulating blood</td>
<td>A X X X</td>
</tr>
<tr>
<td>Implant device</td>
<td>A X X X</td>
</tr>
</tbody>
</table>

**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.

<table>
<thead>
<tr>
<th>Biocompatibility Requirement</th>
<th>Japan MHLW</th>
<th>Korea MFDS</th>
<th>China CFDA</th>
<th>US FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP Test Report</td>
<td>Generally Required</td>
<td>Strictly Required</td>
<td>Generally Required</td>
<td>Recommended</td>
</tr>
<tr>
<td>Finished Device Test: Test article same as proposed device</td>
<td>Recommended, but leveraged testing performed on raw materials as the same as those of the predicate devices can be accepted.</td>
<td>Required</td>
<td>Recommended</td>
<td>Recommended, chemical characterizations of colorants can possibly be asked through 510k, PMA inquiries.</td>
</tr>
<tr>
<td>Test sponsor same as the proposed device manufacturer</td>
<td>N/A</td>
<td>Required</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Time points of Test report issuances</td>
<td>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.</td>
<td>MFDS only accepts test reports that have been issued within the last three years. Otherwise, provide a justification in the notarized certification format.</td>
<td>If test reports were issued prior to 2003, ISO 10993-1 (2003), justifications may need to be provided.</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**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.

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

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

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