

---

---

## **OBTAINING JAPANESE MEDICAL DEVICE REGULATORY APPROVAL: RECENT CHANGES AND THEIR IMPACT ON YOU**

BY MIKE WINEGAR  
TOXIKON CORPORATION  
DECEMBER 1, 2005

### **OVERVIEW**

#### **Japan history, healthcare structure, and economic status**

Japan is a culture that dates back over 9,000 years. Japan has had the Imperial System in place for over 2600 years. The current population is about 130 million people, living in an area roughly the size of California.

Japan is the second largest medical device market in the world. The US enjoys a trade surplus in the medical device sector, and this surplus has been increasing since 1991. US medical device imports in 1997 were over 5 billion dollars, and is approximately 6 times larger now than they were in 1983. The largest device importers are Johnson and Johnson, Boston Scientific, Baxter, Medtronic, Bausch & Lomb, Guidant, Edwards, and Becton Dickinson.

There are over 9000 hospitals in Japan, approximately 84% are publicly held. The majority of these hospitals are losing money. Ninety percent of Japanese belong to one of 3 major insurance groups. They are currently facing a stagnant economy, even showing signs of deflation over the last few years in some sectors. As with most industrial nations, they are also faced with an aging population. Although they currently spend only approximately 50% of what the US does on health care per person, their per capita healthcare expenditure is rising rapidly, and the healthcare system will go bankrupt without fundamental change. One method already in place to try to curb costs is a systematic reduction in device reimbursement costs of 5-7% every two years.

#### **Past regulatory environment for importer and manufacturer**

Japan has had medical device regulations in place since 1960, when the Pharmaceutical Affairs Law (PAL) was amended to include medical devices and cosmetics. Prior to 2000, medical device applications and approvals were generally easy to understand, prepare, and obtain. Broad categories of devices could be applied for and obtained, even if data only existed for a small portion of these devices. It was not uncommon to obtain approvals on certain device models long before they were designed.

Several factors led up to major regulatory changes that began in 2000, with final regulations being adopted April 1, 2005. Implementation of these regulation changes will continue through 2006 and beyond, some good for US manufacturers, and some not.

As mentioned above, there are major cost factors as one primary driver for change. Another major impactor was the “tainted blood scandal” in the late 1980’s, where government regulators delayed the introduction of heat-treated blood products, resulting in the infection of over 1800 hemophiliacs with HIV. Lastly, there have been pressures, both within Japan and from abroad, for harmonization with regulations from the US and Europe, and for enhanced deregulation and competition laws which would speed the approval process in Japan.

### **Current and future regulatory environment**

Major regulatory reform began in Japan in 1985, with the Market Oriented, Sector Selective (MOSS) talks. One of the first topics addressed under MOSS was the ability to use non-Japan clinical data to obtain device approvals in Japan, something that was not allowed prior to the late 1980’s. Although improving, currently only about 20% of submissions relying entirely on foreign data are accepted.

MOSS is now the vehicle for working-level discussions under the Enhanced Initiative on Deregulation and Competition Policy. Other major changes that have occurred are:

- In 1995, in an effort to speed submission reviews, MHW granted the Japan Association for the Advancement of Medical Equipment (JAAME) the authority to perform equivalency evaluation on “Me-Too” devices (those equivalent in design and indication to devices already on the Japanese market).
- In 1997, to further expedite reviews, MHW established the Pharmaceutical and Medical Device Evaluation Center (PMDEC) to perform evaluations, whenever necessary, after investigation by JAAME would indicate a device to not be a “Me-Too” device. In practice, PMDEC often re-evaluated “Me-Too” decisions made by JAAME, resulting in delayed (not expedited) reviews for most devices.

Prior to April 2000, only 2 device categories existed, “Me-Too” and “New”. “Me-Too” devices normally required 4 months for review, while “New” devices normally required one-year review (including a review of human GCP-compliant clinical data). In 1999, approximately 3000 submissions were reviewed in Japan, with 90% judged to be “Me-Too” devices.

In April 2000, several major changes were implemented in the MHW review process. These include:

- The creation of a third device category, “Improved Medical Device”. This is a category between “Me-Too” and “New”, intended to capture those devices that are new device designs for established indications or therapies. Devices in this category include devices with materials/colorants for which there is no precedent approval in Japan, and devices with animal origin materials. Estimated review times for an “Improved” device is one year.
- Under this scheme, JAAME only reviews those devices deemed to be substantially equivalent “Me-Too” devices, and PMDEC only reviews those devices deemed to be “Improved” or “New” medical devices. MHW issued guidance to manufacturers in 1999 (Notification 1677) to aid them in determining the classification of devices prior to submission.
- Submission requirements were also clarified and defined as part of this process. In general, these requirements have increased the need for specific information on all materials used in a device, design specifications for all individual models included in a submission, and copies of manufacturing records for all families of a device included in a submission.

Another major change, implemented in August 2001, is in regard to “GMPi” (GMP compliance of the importer). This requires that the importing office maintain GMP compliance records for every lot of product imported in Japan. This typically includes Receiving Inspection data, product records, sterilization data, and certification that the finished devices meet specifications as submitted and approved in Japan.

Additional changes to the PAL were implemented in 2004 and most recently in April, 2005. These changes are designed to further streamline and clarify the submission and approval process, and are designed to be more in harmony with US and EU systems.

Devices now fall into one of four classes, with Notifications (instead of an approval) only required for Class I devices. There is also the ability of a new MHLW agency, the Pharmaceutical and Medical Device Agency (PMDA), in regard to allowing/appointing Third Party Reviewers to act on behalf of MHLW, similar to the role of a Notified Body in Europe. There is also a new requirement in regard to MHLW (or their designate), performing manufacturing site audits. These audits would be conducted prior to the approval of “identified” (some devices will have review of submitted data only, rather than site audits) Class III-IV medical devices, or at least once every five years.

Also implemented as part of the 2005 PAL revision implementation is the creation of an entity in Japan entitled Marketing Authorization Holder (MAH). In the past, a US manufacturer could either register their products with MHLW directly (Foreign Manufacturer Approval) and appoint a local agent (In-Country Caretaker), or allow

---

an agent/distributor in Japan to register the product in the name of that agent/distributor (Import Approval). With the implementation of the 2005 PAL revisions, the ability to utilize these two systems has changed dramatically, eliminating the roles of In-Country Caretaker and abolishing the Import Approval scheme.

Under the 2005 PAL revisions, a MAH is responsible for all aspects of product quality, registration, and post-market surveillance. The MAH is responsible for obtaining registrations, ensuring the quality systems of the manufacturing facilities, developing release criteria in Japan for each imported product, retention of manufacturing, QC, distribution records, and complaint records, and compliance with Japan vigilance requirements.

Various MHLW offices were also combined in an effort to reduce costs and increase efficiency. Also the submission and GMPi requirements have become more clear, but also more difficult to meet. Lastly, it is documented that MHLW will continue to accept ISO 10993 data, but there still is unique extraction conditions that require additional biocompatibility testing for Japan in the areas of cytotoxicity, sensitization, and hemocompatibility.

It is anticipated that MHLW will increase staffing levels for the various components of PMDA, which will largely be funded through increased user fees to be paid by entities applying for approvals. MHLW has increased user fees from current 703,100 yen for new device submissions to 1,300,000 yen, nearly doubling the fees in almost all categories. Future fee schedules for 2006 show further increases. For example, if a company has filed a Class III device with clinical trials in 2005, they have incurred filing fees totaling 5.8 million yen (approximately \$46K).

In summary, there are many uncertainties regarding these recent changes and their impact on application requirements as well as review timelines. The US Medical Device industry also maintains concerns regarding the following areas:

- Lack of cycle time review commitments until March 2009, potentially allowing excessive review times in the first few years of implementation
- Potential increase in testing requirements
- Lack of consistency between local MHLW offices in interpretation of MHLW regulations regarding issues surrounding standard and test method
- Proposed inspection of foreign manufacturers without appropriate staffing level
- Lack of clarity in areas of consultation for clinical trials
- Increase in review/consultation fees along with introduction of post-marketing safety fees

## **Clinical Trials**

Japanese GCP requirements have many similarities to requirements in place for the US and Europe. Basic functions of the Sponsor, Investigators, Informed Consent, Record Retention, and IRB's are nearly identical to requirements currently in place for the US.

One major difference pertains to the role of the Chief Investigator. For trials run in Japan, the Chief Investigator is responsible for the supervising all aspects of the trial, training and overseeing other physicians involved in the trial, and generating/signing the study final report. These requirements are in place whether the study is conducted in Japan or elsewhere.

Also in contrast to the US, procedures governing the generation, submission, and eventual approval of clinical data are not consistent. Many of these items are open to interpretation by reviewers at MHLW; so basic items such as sample size, statistical power, and success criteria can be open for discussion at any time during review of trial results. In general, MHLW reviewers are reluctant to make firm commitments in regard to submissions requiring clinical data. If FDA has approved a given product, and the data used to obtain this approval is also used for MHLW submission, the chance of a positive outcome is increased. In the situations where EU data is used, data that has not been statistically analyzed, US data from a study that did not result in an FDA approval, or submissions of only a portion/interim analysis of a study is utilized, the chances of a positive outcome diminish greatly.

In all cases, there are some unique GCP requirements to be aware of. In general, these relate to the MHLW desire to have all clinical data be GCP compliant. In other words, for 100 percent of the data on 100 percent of the patients, each protocol deviation or missed entry must either be corrected, or the individual impact of that item on the final report must be justified. If proper justification of this impact cannot be made, then this patient has to be removed from the primary analysis. If enough of these types of situations occur, it could have a very negative impact on patient numbers and statistical outcome.

It is therefore important to understand this difference prior to execution of any study where the data may be used for submission purposes in Japan.

MHLW will also require a final report signed by the Chief Investigator, copies of the entire database, copies of all site binders (including IRB approvals, Investigator CV's, site qualifications), all protocol revisions with rationale for revision and poolability of data. For any patient that has an AE of any type, a complete copy of that patient's CRF will be required prior to submission. Approximately 3 months after submission, any remaining CRF's must be made available, although may not be reviewed as part of the approval process.

---

## IMPLICATIONS FOR YOUR MEDICAL DEVICE COMPANY

### Regulatory

Preparation of submissions and data specifically for Japan  
More complex submissions  
Greater levels of material and specification data needed than for US and EU submissions.  
Deeper understanding of QA, clinical, preclinical, activities  
Understanding of reimbursement routes/categories prior to submission  
Need to inform Japan, in advance, of any change that will impact any submitted/approved information.

### QA

Need to provide RI and manufacturing data, certification of sterility, certification that product meets spec, with each lot shipped to Japan  
Need to conduct additional biocompatibility testing, supplement to ISO 10993, to meet Japan Pharmacopoeia requirements. Need to repeat key tests yearly.

### Research and Development

Need to be aware of predicate materials and colorants approved in Japan.  
A new colorant or material will change a device from a “me-too” to an “improved”.  
Advantageous to build Japan-specific items, such as material identification and biocompatibility test samples, into the PDP process

### Sales and Marketing

More extensive submission requirements will mean later submission dates for Japan  
Longer review times, plus the need to obtain reimbursement approval after regulatory approval and prior to launch will require estimates of the time period between submission and launch to be increased

### Manufacturing

Need for access to procedures, manufacturing build data, and QC inspection data for each product family submitted.  
Ongoing need for copies of manufacturing data to verify that product meets specs approved in Japan

### Clinical Research

Need for GLP compliant animal data for submissions requiring animal data  
Human clinical data used for submission must be GCP-compliant, and study design must statistically meet a predetermined endpoint.  
Need for GCP-compliant data (to the individual patient level) for submissions requiring human clinical data. Also require final clinical report (of GCP compliant patients), database, copies of some/all CRF's and Site Binders.

### IT

Need for Japan to have electronic access to manufacturing and QC records for all lots sent to Japan  
Need for Japan to have electronic access to all prints, specifications, procedures, and Change Orders.

### CONCLUSIONS and RECOMMENDATIONS

Costs, complexity, and timeframes increased, reimbursement decreased, but still second largest global device market  
Need to develop a Project with a Team Leader to implement/integrate above items into **your** systems and procedures