Proposals

Issues Regarding Regulations for Medical Devices in Japan and Solutions Thereof

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Regulatory Affairs and Quality Assurance (RAQA) Committee
American Medical Devices and Diagnostics Manufacturers' Association (AMDD)

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Executive Summary

Proposals regarding revisions in Pharmaceutical Affairs Law for Medical Devices (including *in-vitro* diagnostic devices)

Proposals regarding the entire Pharmaceutical Affairs Law

- Descriptions of each provision of the Pharmaceutical Affairs Law should be divided into "drugs, quasi-drugs and cosmetics" and "medical devices."
- The requirements of ISO 13485 should be applied without any modification.

Proposals on individual provisions

Article 1 (Objective)

- Addition of two perspectives: "expedited introduction" of medical devices, and "contribution to public health."
- Replacement of "*yukosei* (efficacy)" by "*seino* (effectiveness)" because the former conjures up drugs.

Article 12-2 (Requirements for license)

- Integration of GVP and GQP because quality issues are inextricably linked to safety issues.

Article 13 (Manufacturing business license) Article 13-3 (Accreditation of foreign manufacturers)

- Transition of the license and accreditation systems for manufacturers, regardless of domestic or foreign, to a registration system by making QMS compliance a mandatory requirement.

Article 14 (Marketing approval)

- Expansion of the current concept of "product-by-product" to establish a system to approve and accredit medical devices by their operating principle.
- Concurrently, adoption of the least burdensome approach to evaluate devices based on the minimally required documents from design control rather than "identifying" medical devices as used for drugs.
- Facilitating timely improvement [of medical products] by limiting of the scope of partial amendment applications through proper implementation and establishment of QMS (particularly design control) in lieu of "product specific" QMS audit.
- Abolition of reliability inspections other than GCP and GLP inspections to avoid redundancy with QMS inspection on design control.

Article 23-2 (Marketing certification of designated controlled medical devices)

- Delegation of review of low-risk products (correspond to general medical devices), along with QMS audits, to recognized (third-party) certification bodies

Article 63-2 (Descriptions on package inserts)

- Adoption of a system of package inserts in considering user benefits (e.g. provision in the form of electronic files using the Internet, use of instruction manuals as a substitute)

Introduction

The current Pharmaceutical Affairs Law (Law No. 145, 1960) was enacted with its main objectives to ensure quality and efficacy of pharmaceuticals and regulate their sales, almost concurrently with the national healthcare system, which was established with the aim of contributing to improving social security and public health in 1958.

Medical devices were originally regulated as medical tools (*iryo-yogu*) and the regulations for drugs were applied, as quasi-drugs and cosmetics were. Since then, drugs and medical devices whose characteristics are different each other have been regulated under the same law.

Medical devices cover a broad range of products, ranging from scalpels and tweezers to diagnostic imaging apparatus and implantable devices. They were originally developed as tools for doctors and other healthcare professionals to treat and diagnose patients. While a drug is developed with focus on responses (effect and efficacy) to its active ingredient in the body and unexpected reactions (adverse drug reactions) mainly aiming at developing a superior, innovative active ingredient (natural scientific approach), a medical device, which is designed and evaluated based on the purpose of use (development concept), is provided to medical professionals and facilities while undergoing continuous improvement based on feedback from healthcare professionals who have used it in clinical settings (applied scientific approach). Such improvements to devices are made in various aspects, from quality and safety to usability, which are built on close collaboration between healthcare professionals and companies engaged in the development.

Just as development and improvement cannot be ensured by companies alone, in order to ensure the safety of medical devices, a postmarket vigilance system, including medical societies as users, is necessary. The current attempt to ensure safety only by enhancing the premarket review system hampers the development of medicine using medical devices and public access to advanced or appropriate medical technology.

In this context, the Regulatory Affairs and Quality Assurance (RAQA) Committee of the American Medical Devices and Diagnostics Manufacturers' Association (AMDD) decided to visualize casual factors to identify obstacles caused by the current Pharmaceutical Affairs Law in ensuring quality and safety of medical devices and make specific proposals for new medical device regulations.

The current Pharmaceutical Affairs Law regulates many aspects of the process from development phase of a medical device, approval application, review, approval of the Minister of Health, Labor and Welfare to finally launching the product. In the present analysis, issues that need to be addressed in each phase are classified into seven categories (design control/risk management, quality management system (QMS), software/IT, clinical evaluation, premarket review, postmarket safety management (GVP), and business licenses, as shown in **Figure 1**.

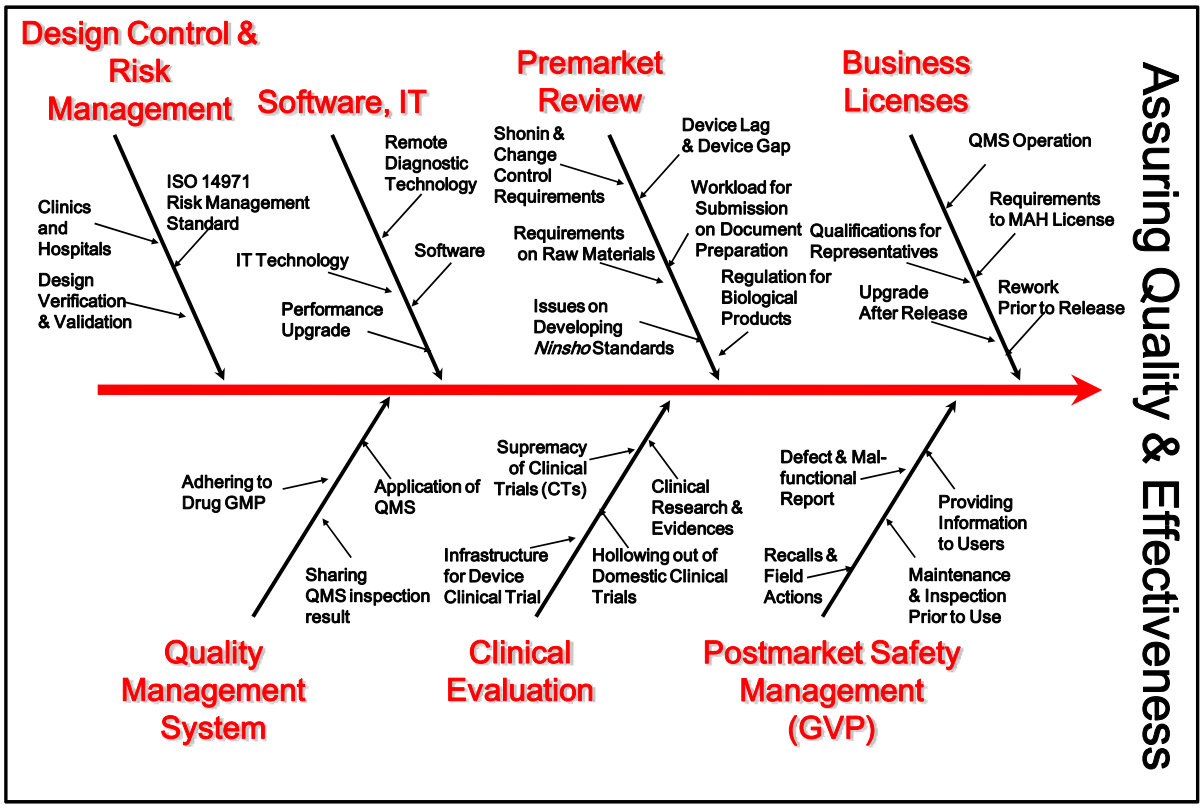


Figure 1: Issue analysis on medical device regulations

In the following pages, regulation-related issues and proposals to solve these issues will be described in each chapter. In the Fish Bone Charts in each chapter, issues are preceded by a black dot and proposals by a blue arrow.

1. Design Control/Risk Management

Ones of the most important factors to ensure “quality” and “safety” of medical devices are “design control” and “risk management.”

The design of a medical device is only started after deciding the intended use/purpose. In other words, a medical device is designed on the premise that “it will be used” and “there will be users.” Therefore, the therapeutic and diagnostic needs of doctors and other healthcare professionals are important inputs in designing medical devices and their feedback information is essential in the process of design evaluation. It is no exaggeration to say that “medical devices are delivered from the sites (Field).” Also in postmarketing phase, feedback from medical facilities, including safety information, is necessary for improving safety and better effectiveness of the medical device. It is important that such information should be reflected promptly to improve the medical device.

Medical devices provide its effectiveness when used by healthcare professionals. Injuries associated with a medical device may occur on the patient through the intervention of its user or an unintended use. In the design process of a medical device, therefore, possible hazards are identified and possible risks are estimated using risk management methods. Based on the incidence of the identified risks and the severity of possible injuries, the risks are assessed by risk analysis methods, such as the FMEA (Failure Mode and Effect Analysis), and how to address each of them is discussed. The device is thereby designed in such a way as to minimize the risks to the lowest acceptable level (risk reduction measures).

1) Issues regarding design control and risk management

(1) Medical facilities and design verification

i. Participation by clinical healthcare professionals in the development process and relevant laws and regulations

Based on the establishment of the “Council on the Realization of the New Growth Strategy” (Cabinet decision on September 7, 2010) under the current administration in Japan, the “Medical Innovation Promotion Office,” consisting of public and private members, was established to promote medical research and development to commercialize innovative pharmaceuticals and medical devices developed in Japan and also to realize various issues regarding the new growth strategy in the healthcare field. The Medical Innovation Promotion Office has started investing research and development funds to promote research and development efforts engaged jointly by government, academia and industry, from basic research through to commercialization in a seamless manner, and to improve research infrastructure.

Medical devices provide its effectiveness when used in clinical settings and are subject to continuous improvement [of medical devices]. For this reason, if there is a legal framework to evaluate the clinical effectiveness of a medical device with a method other than clinical trials before marketing, it would contribute to timely improvement. However, there are no regulations at present to maintain such a development speed. In addition, support documents required for premarket review include validation of the manufacturing process on the premise that the final product is actually manufactured with the process and the [delayed] timing for approval application hampers to promote continuous product development and improvement.

ii. Experience of reviewers on design process

The “product realization” section of ISO 13485 defines a series of process from designing to evaluating and validating a medical device. In particular, the followings are required as inputs into design and development:

a) functional, effectiveness and safety requirements, according to the intended use;
b) applicable statutory and regulatory requirements;
c) information derived from previous similar design concept, if applicable;
d) other requirements essential for design and development, and;
e) output(s) of risk management.

Hands-on experience on this process is considered to help understand appropriately what should be reviewed and confirmed in premarket reviews. At present, however, there seems to be few staff that has actually experienced these processes among reviewers in the Office of Medical Devices of the Pharmaceuticals and Medical Devices Agency (PMDA).

(2) Risk management standard: introduction of the concept of ISO 14971

Risk management methods for pharmaceuticals include pharmacovigilance and pharmacoepidemiologic assessment. As for medical devices, ISO 14971 provides the requirements for the application of risk management, which are required to implement in the design and development (product realization) in the processes of the quality management system: QMS (ISO 13485).

Risk assessment of drugs is made by effective use of inputs from premarket nonclinical evaluations and premarket clinical studies conducted in accordance with strict protocols as well as of various kinds of epidemiological and postmarketing safety information gathered from patients treated with the drug in the postmarketing sites. As for medical devices, in addition to secondary injuries caused by the use intended in the design process, there are risk factors that should be assessed in relation to all factors associated with healthcare professionals who use the device as well as factors included extensively in the healthcare environment.

Although companies engaged in design and development of medical devices should be responsible for taking appropriate measures to reduce these risks as required by the Product Liability Law, the implementation of such measures should not be included in review for approval and other premarket reviews. At present, however, companies are required to include information on risk reduction measures in premarket application documents.

2) Proposals for the aforementioned issues

(1) Medical facilities and design verification & validation

i. Participation by clinical healthcare professionals in the development process, and relevant laws and regulations

Our expectations for the role of the Medical Innovation Promotion Office are very high as the “control tower” that aims at creating innovative medical devices realized in Japan. However, since the goal of its activity is to create innovative medical devices in 10 to 20 years, and further in 50 years, it is important, in the short term, to consider how “premarket review” should be conducted in order to rapidly implement improvement in the design and development according to the characteristics of each device. (Specific proposals are detailed in “5. Premarket review.”)

As to how premarket evaluation in clinical settings should be, it is also necessary to discuss the establishment of a legal framework that allows healthcare professionals in clinical settings to participate in the evaluation of the clinical effectiveness of a medical device as an alternative to “clinical trials.”

ii. Experience of reviewers on design process

Possible solutions may include hiring staff that has experienced the manufacturing process (design and development of products) in medical device or other industriesy, as reviewers, or exchange between reviewers and staff of these industries. It is also necessary to consider introducing a “practical” educational program on design process to deepen reviewers’ understanding of the appropriate evaluation of data generated in the design process as part of premarket review materials. This will help prevent reviewers from requiring excessive or irrelevant data to evaluate products that are not included in the design process.

These efforts will make it possible to adopt the least burdensome approach.

(2) Risk management standard: introduction of the concept of ISO 14971

To be prepared for QMS conformity assessment, it is important, in terms of product effectiveness and safety assurance, to adopt the ISO 14971 standard on global implementation, to implement risk management in the design control process properly in compliance with the ISO 14971 standard, and to make sure that, during the product life cycle, risk management is properly implemented and managed and controlled based on continuous input of postmarketing information (quality information, GVP, etc.).

The current issues regarding design control and risk management of medical devices and proposals to solve the aforementioned issues are summarized in **Figure 2**:

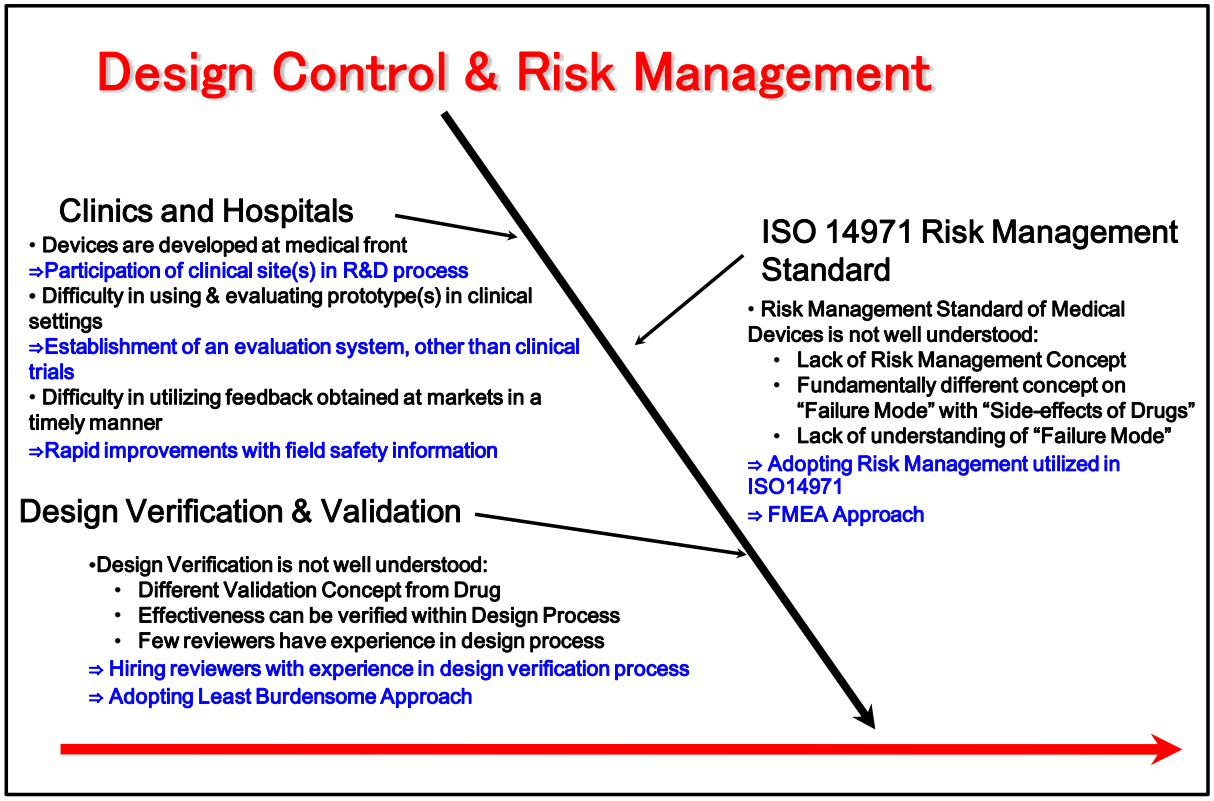


Figure 2: Issues and proposals regarding design control and risk management of medical devices

Summary of proposals: It is necessary to convert the approach of reviewing medical devices from that in intended for drugs which evaluates "substances" or "mechanism of action" from "micro" standpoints into the approach exclusively dedicated to medical devices which evaluates the appropriate functioning of the "design control process" from "macro" standpoints.

2. Quality Management System (QMS)[1]

QMS is a concept of quality assurance different from that in defined in the medical device GMP[2], the medical device GMPI[3]or that is applied to individual drug products (GMP regulations). Since the revision to the Pharmaceutical Affairs Law (PAL) in 2005, it has been required to implement a quality management system that is in compliance with the MHLW Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Medical Devices and *In-vitro* Diagnostic Reagents (hereinafter referred to as "QMS Ordinance"), providing unified regulations on quality management for both domestically manufactured and imported products. Before the implementation of the revised PAL, the medical device GMP had been applied to domestic products, and the medical device GMPI to imported products. The medical device GMP and GMPI enforce similar requirements to the current pharmaceutical GMP[4], such as implementation of the manufacturing and (in process) inspection processes defined in the "Device Master Record" to ensure the quality and safety of the product and emphasis on verification of compliance in shipping inspections. The current QMS Ordinance provides a method for quality assurance as follows: the quality and safety of a product is evaluated in the design and manufacturing processes, and after the validity of the evaluation methods applied is verified by various validation methods, the quality is assured by checking each control item that has been validated. This method complies with an international standard for medical devices "ISO13485:2003[5] Medical devices – Quality management systems – Requirements for regulatory purposes" (hereinafter referred to as "ISO 13485), which is widely recognized abroad, and aims at conforming to international requirements. However, the concept of manufacturing and quality control before the revision to the PAL is still followed in implementing QMS in Japan, and the QMS Ordinance applies to a segment (divided according to addresses of manufacturing sites), not to the governing body of the management that implements the QMS. In addition, although QMS inspection should be conducted on the overall "system," it is conducted on individual products as an assessment (inspection) that is a part of premarket reviews, which is unique to Japan. The concept of the ISO 13485 fundamentally differs from that of the current pharmaceutical GMP implemented in Japan in many ways such as the way of controlling design and development (design control, design verification, design validation) and the way of implementing quality assurance.

1) Issues regarding QMS

In the PAL revised in 2005, regulations for manufacturing and quality control were changed from GMP and GMPI to QMS (Quality Management System). However, there are substantial problems associated with QMS application, implementation and inspection based on ISO 13485, the global standard used in EU, U.S and etc., as shown below:

[1]QMS: Quality Management System, is a management system to direct and control an organization with regard to quality (JIS Q 9000: 2006). In this document, QMS refers to the standards for manufacturing and quality control for medical devices and *in-vitro* diagnostic reagents. [Ordinance on Standards for Manufacturing Control and Quality Control for Medical Devices and *In-vitro* Diagnostic Reagents, MHLW Ministerial Ordinance No. 169 dated December 17, 2004]

[2] Medical device GMP (Good Manufacturing Practice): Regulations for manufacturing and quality control of medical devices, MHW Ministerial Ordinance No. 40 dated June 26, 1995

[3] Medical device GMPI (Good Manufacturing Practice by Import): Regulations for import and marketing control and quality control of imported medical devices, MHW Ministerial Ordinance No. 63 dated June 2, 1999

[4]Pharmaceutical GMP: Standards for manufacturing and quality control required for pharmaceutical manufacturers, which are different from QMS, the standards for manufacturing and quality control for medical devices. [MHLW Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs, MHLW Ministerial Ordinance No. 179 dated December 24, 2004]

[5]An international standard for quality assurance of medical devices, where some of the requirements of ISO 9001 are omitted and requirements specific to medical devices are added.

(1) Concept of implementing QMS at manufacturers

The Japanese QMS regulations are required to each manufacturing location, unlike ISO 13485 where a series of processes from design and development for product realization to postmarketing activity is regarded as a system to which the standard is applied. More specifically, if "outsourced sterilization facilities," "design centers," and "testing facilities" are located in different sites, inspection is conducted separately in each site. QMS inspection in Japan is divided by process, not by system as stipulated in ISO 13485.

(2) Issues regarding product reviews and QMS audit conducted upon review of application for approval and certification

QMS: ISO 13485, the standard that clarifies mutually related processes as one system to understand and govern the system, and the pharmaceutical GMP, the standard for manufacturing and quality control of individual products, conflict with each other in their approach to quality control. Nonetheless, the QMS Ordinance follows the concept of the pharmaceutical GMP, which is the standard for quality assurance for products alone, and product specific QMS inspection is still conducted. While a more flexible approach has been adopted since the issuance of "Guidance on application for QMS conformity assessment" (MHLW *Yakushokukanmahatsu* No. 0401-7 and *Yakushokukihatsu* No. 0401-2, both dated April 1, 2011), the product specific QMS inspection system is still conducted upon review of application for approval or certification.

(3) Issues regarding full mutual recognition of QMS inspection results obtained in the past

While Notified Bodies perform ISO 13485 conformity assessment in foreign countries, QMS inspection under the QMS Ordinance is performed by three different authorities (PMDA, local governments and Registered Certification Bodies) according to the medical device classification. Under this system, a manufacturing facility that manufactures products in different classifications is required to undergo QMS inspection for each application of each product, resulting in many QMS inspections per year by different authorities. This imposes significant burdens on both inspectors and companies. In particular, PMDA performs conformity assessment of medical devices of class 3 or higher, whose risks are relatively high, with its limited number of inspectors. The ratio of on-site assessments of such high risk devices at overseas manufacturing sites is extremely low in comparison with that of certified products whose risk is considered relatively low.

Since QMS is the key framework to ensure the quality of a medical device, it is considered necessary to assess the degree of implementation of QMS assessment of new medical devices whose risk to the human body has not been elucidated, in parallel with premarket review. However, due to the limited resources within PMDA, it is not possible to conduct sufficient assessment. While the "Guidance on sharing of results from QMS inspection and surveillance assessment" (MHLW *Yakushokukanmahatsu* No. 0401-12 and *Yakushokukihatsu* No. 0401-7, both dated April 1, 2011) has allowed different authorities to share results from their assessments, it is also necessary to clarify respective roles of QMS inspections for system and for each product as well as surveillance assessment, to clarify which part of results from each assessment can be shared and what items should be assessed by each authority, to improve the efficiency of assessments, and to take more fundamental measures to promote sharing assessment results.

2) Proposals for the aforementioned issues

(1) Concept of implementing QMS at manufacturers

The target of QMS conformity assessment should be the "manufacturer[6] in line with the concept of ISO 13485," the main body that implements a QMS. The aim of QMS conformity assessment is to verify that the organization has the ability to provide medical devices that consistently meet customer requirements and regulatory requirements applied to relevant services. Marketing Authorization Holders (MAHs) are required to confirm the conformity before introducing a product into the market. By stipulating that QMS inspection procedures and authorities' qualifications (called "competency" in ISO 13485) should meet the requirements of ISO 17021[7], an international standard, variation among authorities can be eliminated and full mutual recognition of inspection results can be allowed, and thereby results from QMS assessment (inspection) by Notified Bodies (different from "Recognized Certification Bodies" that are currently in charge of certification reviews. They are organizations that can perform verification of the QMS conformity under ISO 17021) can be used more effectively.

(2) Separation of QMS inspection and application review for approval or certification

QMS conformity should be verified upon applying for approval or certification of a product by attaching a certificate of QMS conformity that has been verified by a certification organization in compliance with ISO 17021 as described above (more specifically, a certificate of conformity to ISO 13485) to the application document. As an exception, QMS inspection of unknown risk level products, such as new medical devices whose effectiveness and safety can only be reviewed by on-site assessment, is conducted in the review for approval. This separation between product review and QMS assessment (inspection) allows securing number op certification organizations that comply with ISO 17021 as a resource for QMS conformity assessment. This will also reduce complexity and burden experienced by MAHs and manufacturers of medical devices through having redundant QMS assessments conducted by multiple authorities. Concurrently, this will allow the limited resource of reviewers of PMDA to be engaged in assessing the quality and safety of products with highly probable risks in review for approval.

(3) Full mutual recognition of QMS inspection results obtained in the past

Full mutual recognition of QMS inspection results obtained by certification organizations that comply with ISO 17021 should be institutionalized so that manufacturers whose conformity to QMS requirements has been verified are exempted from "product specific QMS inspection" for every application of approval or certification. Effective use of certification results by Recognized Certification Body should be promoted.

The practices inconsistent with the international standard ISO 13485 described above should be abolished and the concept of the GMP regulations should be departed from, and thereby a system should be established to enforce relevant laws and regulations that are consistent with international standards in order not to lag behind foreign authorities.

[6] Manufacturer: Corresponding to "organization" in ISO 13485

[7] ISO 17021: Conformity assessment – Requirements for bodies providing audit and certification of management systems

The current issues regarding QMS of medical devices and proposals to solve the aforementioned issues are summarized in **Figure 3**:

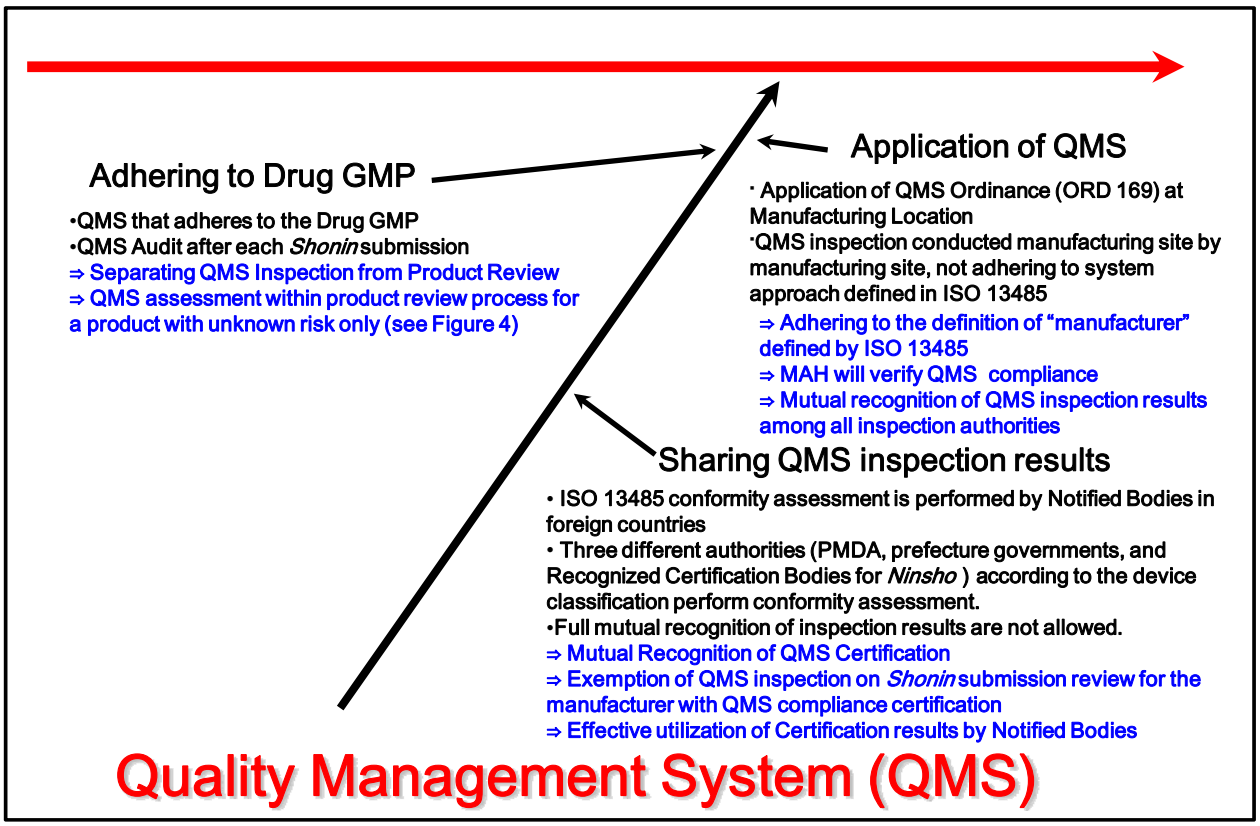
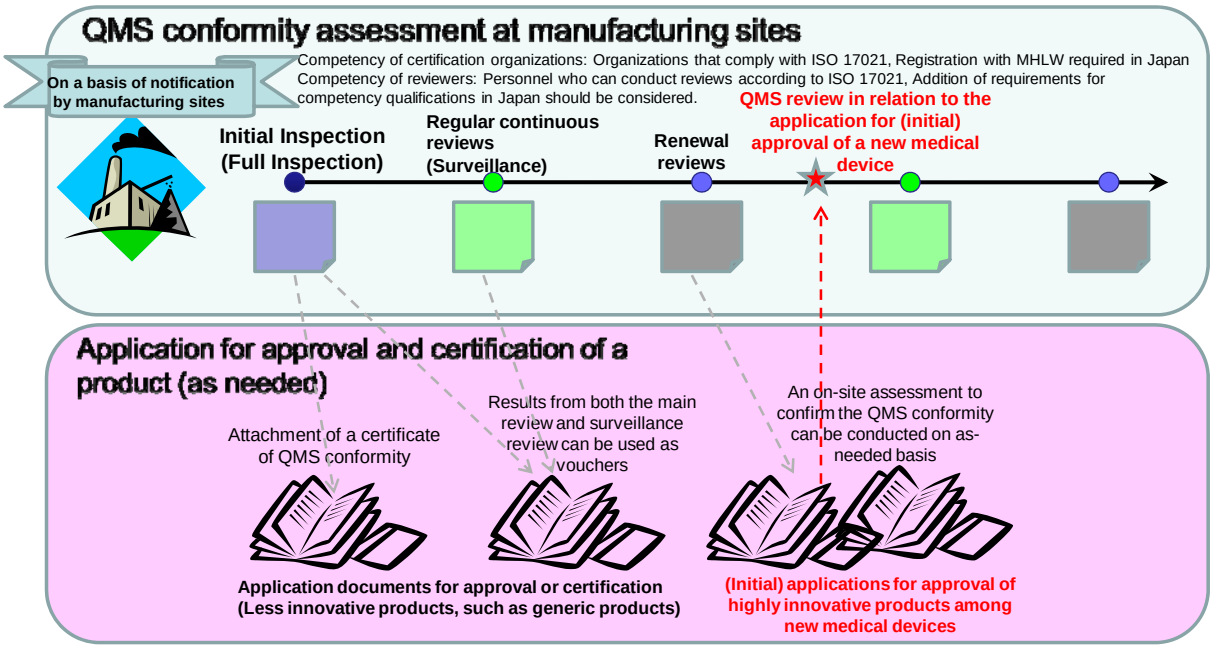


Figure 3: Issues and proposals regarding QMS for medical devices

* Corresponding to "organization" in ISO 13485

Approval review processes can be made more effective by being implemented along with a QMS and, concurrently, safety can be improved. In *The 9th Teiki Iken Kokan Kai* (Reriodic Regulatory Round-table Meeting) on medical device regulations on July 12, a new proposal on QMS review and approval review processes shown in **Figure 4** was presented.

New proposal for QMS review scheme



QMS conformity assessment at a manufacturing site conducted in accordance with ISO 17021 and effective monitoring of design and manufacturing control by verifying the conformity on a regular basis will realize effective manufacturing control.
In addition, a regulatory approval for a minor change will be unnecessary, making timely improvement possible.

Figure 4: New proposal on QMS review and approval review processes
（Source: Materials submitted by AMDD at The 9th Periodic Round-table Meeting for medical device regulations）

Summary of proposals: QMS conformity assessment at a manufacturing site conducted in accordance with ISO 17021 and effective monitoring of design and manufacturing control by verifying the conformity on a regular basis will realize effective manufacturing control.
In addition, regulatory approval for minor change control will be unnecessary, making timely improvement possible.

3. Software and IT

The current Pharmaceutical Affairs Law was enacted in 1960, when analog technology was in full swing in the field of medical devices as in medical treatment. It was totally inconceivable at that time that people could enjoy benefits from information technology (IT) widely available today in the healthcare field, including remote control surgery, high-resolution three dimensional diagnostic imaging, and remote diagnostic imaging.

In subsequent years, efforts were focused on safety enhancement, global harmonization and introduction of third-party certification systems, and in 2005, the revised Pharmaceutical Affairs Law was enforced. By that time, major GHTF[8] countries, such as EU in 1994 as a starter, followed by the U.S. (1998), Canada (1999) and Australia (2005), had started preparing software-specific regulations. Despite these overseas regulatory responses, even in the revised Pharmaceutical Affairs Law, the outdated regulatory framework where software is approved and certified only along with a PC or workstation on which it is installed was not eliminated.

Today, IT strategies for medical devices have become an extremely important issue, based on efficiency improvement of medical institutions, information provision to patients, growth of the medical devices market, and close relationships with the IT industry. While minimum regulatory requirements to ensure medical safety are essential, it should be avoided to hamper the development of the medical devices industry in Japan due to excessive regulations.

1) Issues on software and IT

(1) Regulating software alone under the Pharmaceutical Affairs Law

To receive marketing approval in Japan for an application software product that has been approved as a medical device overseas, the device where the software is installed must be included in the application for approval or certification. It is not permitted to sell software.

(2) Rules for performance upgrade

The interpretation that software installation should be performed under General Manufacturing License because it is regarded as a manufacturing activity is far from the situation in real world where ordinary people purchase software on a daily basis and install it by themselve. Sales of software downloaded online have become daily experience in other fields than the medical devices field. While some medical device software products[9] are also sold online in foreign countries, it is not allowed in Japan.

(3) Regulating clients of general-purpose IT under the Pharmaceutical Affairs Law

It is interpreted that image display devices for diagnostic imaging, including remote diagnosis, must be categorized as medical devices. It is also interpreted that, in cases where a request for an imaging diagnosis is received from a medical facility without any specialists both in Japan and abroad or a request is made from a domestic facility to an overseas specialist, an image display device used for handling image information for diagnosis must be the one that has been approved, certified or registered as a medical device. However, with today's advanced information technology, it is technically possible even for clients of general-purpose IT system (smart-phones, tablet-type computers (terminals)) to be equipped with these functions. It is therefore time to re-consider the framework for "medical devices" that are regulated under the current law.

[8] GHTF: Global Harmonization Task Force

[9] Example: With regard to addition and change of software used to add a synchronization mode to an artificial respirator, such software to be installed on devices at medical institutions via the Internet is legally sold in the United States. In Japan, however, the installation of such software requires approval as a partial-approval change: The software program should first be downloaded onto a special recording media and then an application for approval should be made.

(4) Border between medical devices and general-purpose electronic devices

The distinction between medical and general-purpose devices has become less clear due to the advancement in information technologies. For example, image display devices are classified as general-purpose devices as long as they are not used for diagnosis but only used for displaying images as a means of communication with patients as part of the function of electronic patient record or for retrieving images on a tablet-type computer; and as medical devices when used for diagnosis. The current rules and regulations have become inconsistent with current business environment.

2) Proposals for the aforementioned issues

(1) Regulating software under the Pharmaceutical Affairs Law

Rules should be changed to allow software alone to be approved or certified by defining the specifications of the device on which the software is installed and to exclude devices from requiring approval or certification. This will enable to address the current situation where it has become extremely difficult to limit devices on which software is installed as information technology is advancing.

(2) Rules for performance upgrade

Software installation no longer require special skills or devices. It is therefore no longer need to regulate the installation of software on general-purpose IT devices as a manufacturing activity. In the information technology infrastructure of medical institutions, rules should be changed to allow users, regardless of the licenses they are granted, to install software under the responsibility of the MAH, either from a medium or the Internet.

(3) Regulating clients of general-purpose IT under the Pharmaceutical Affairs Law

In cases where remote image diagnosis is performed, the doctor performing the diagnosis should be allowed to use, at his/her discretion, an image display device that does not fall under a category of medical devices.

(4) Border between medical devices and general-purpose electronic devices

Taking into account the current circumstances where medical devices and IT devices cannot be clearly differentiated, doctors should be allowed to use, at their discretion, any image display device, regardless whether medical device or non-medical device, on the condition that the device meets certain predefined specifications.

The current issues regarding software and IT for medical devices and proposals to solve the aforementioned issues are summarized in **Figure 5**:

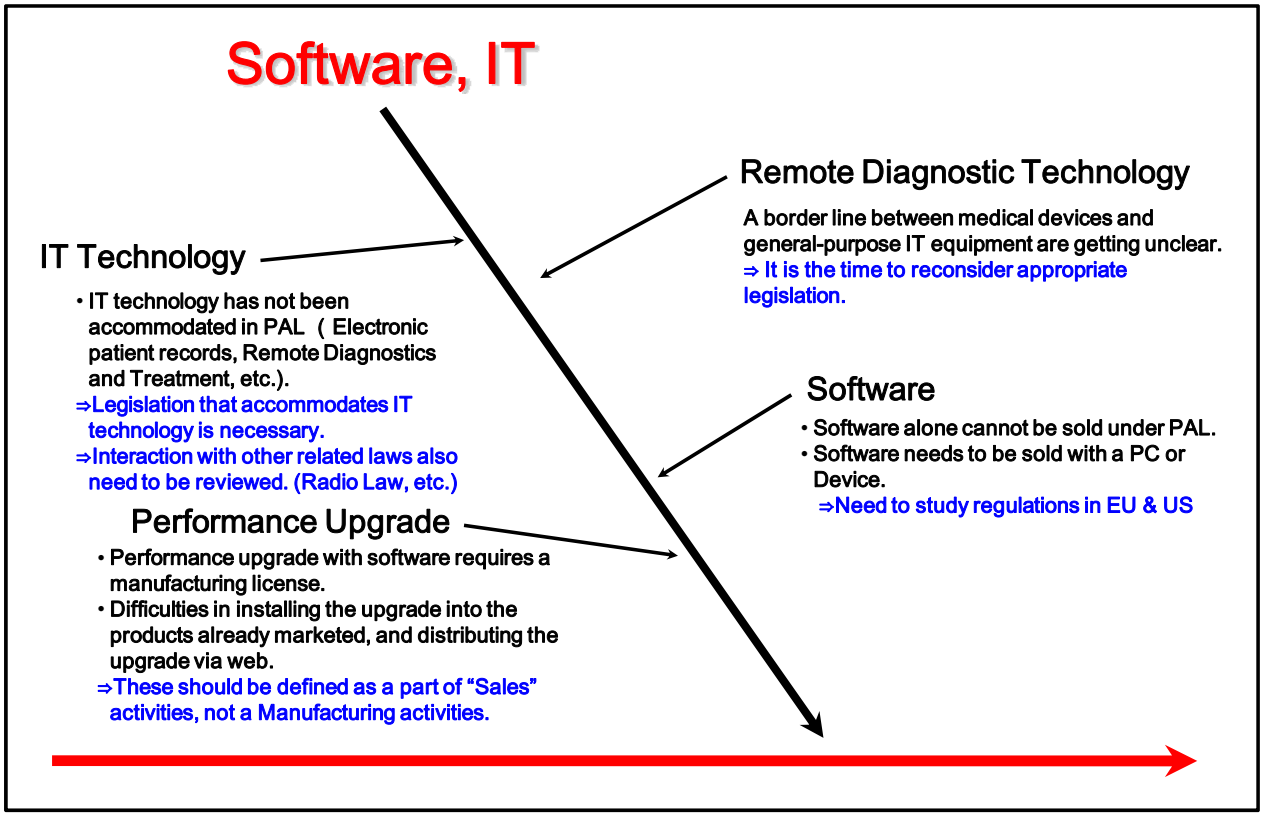


Figure 5: Issues and proposals regarding software and IT for medical devices

Summary of proposals: Information technology is making a remarkable progress today, allowing a speedy diagnosis and treatment of disease with significantly high precision. Legal systems and regulations that allow patients and healthcare professionals to fully enjoy the benefits provided by information technology are required in Japan.

4. Clinical Trials

Clinical trials are performed to verify the efficacy (effectiveness in the case of medical devices) and safety of the target device to be studied. Whether or not clinical trial data is required to apply for approval of a medical device should be determined based on "Necessary Scope of Clinical Investigation Data on Medical Devices" (MHLW *Yakushokukihatsu* No. 0804001 by Chief of Medical Device Evaluation and Licensing Section, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, dated August 4, 2008). This notification states as follows: "When the clinical efficacy and safety of a medical device cannot be evaluated based only upon the results of non-clinical investigations such as performance tests and animal tests, or existing literature, etc., a clinical study must be conducted …" Thus, it can be interpreted that a clinical trial of a medical device should be conducted when evaluation is not possible based on already existing results from clinical trials and appropriate performance tests, or other non-clinical studies, or literature.

This is the concept of "*rinsho hyoka* (clinical evaluation)[10]," which is adopted for medical devices because the characteristics and the significance identified by clinical trials differ between pharmaceuticals and medical devices.

The effectiveness of most medical devices does not mean the efficacy of the device itself but the efficacy of the treatment method, which is fundamentally different from the concept behind drugs that a drug itself exerts efficacy. An implantable device itself can be considered as a treatment method but its efficacy and safety depend on the user (operator). The following are the characteristics of drugs and medical devices:

Drugs generally circulate throughout the body in the bloodstream, metabolized at the tissue, cellular and molecular levels, and excreted outside the body, although there are differences in the time of efficacy and the way of absorption depending on the administration route, whether oral or parental (e.g. intravenously). The drug efficacy can be sustained to some extent by controlling the speed of metabolism but metabolites sometimes exert the intended effect, making the mechanisms of action of drugs complicated. Drugs circulate in a "black box" of the body, change its form through metabolism, and reactions (effects and adverse drug reactions) caused by drugs depend on individual differences. For these reasons, drugs must be studied in human subjects.

Medical devices, on the other hand, maintain a stable appearance, except for some special examples[11]. They act mechanically, electrically, or physico-chemically. Their effectiveness is evaluated along with their method of use. In addition, effectiveness and safety of their use are largely dependent on the users' experience and skills. Generally, in evaluating effectiveness of devices, bench testing tends to be more appropriate than clinical trials, or other non-clinical studies are often sufficient.

Table 1 shows the summary of the differences between drugs and medical devices to be considered in conducting clinical trials.

[10] The term "*rinsho hyoka*" was employed as a translation for the title of the document "Clinical Evaluation" (SG5/N2R8) created by GHTF (Global Harmonization Task Force). The concept of "*rinsho hyoka*" is described in the "Guidance for preparation of materials for consultation on clinical evaluation (draft)" and "Examples" in the website of the Pharmaceuticals and Medical Devices Agency.

[11] Special examples of medical devices whose appearance change include bioabsorbable materials and cultivated cells, and examples of medical devices whose appearance does not change but their coating material does include medical devices coated with a drug.

Table 1: Differences between drugs and medical devices to be considered in conducting clinical trials (general examples)

	Drugs	Medical devices
Method of use	Oral Parental (intravenous, rectal, sublingual, topical)	Wide-range of use (Depends on knowledge and skills of users)
Main subject to be evaluated	Principal agent	The entire components/subsystems
How effects are exerted	Biological reactions (absorption, distribution, metabolism, excretion)	Physico-chemical, mechanical, and electrical reactions
Scope of effects	Systemic	Topical
Duration of effect	The effect will disappear. Long lasting effects are dangerous.	Single or repeated use Long-term use may be needed.

The differences shown above can result in problems specific to medical devices in conducting clinical trials. The following are such problems and our proposals to address them:

1) Issues regarding clinical trials of medical devices

(1) Supremacy of clinical trials

The safety of a medical device is achieved by the establishment of and compliance with the quality level desired and a clearly defined method to use, which is different from drugs which inherently have adverse effects. However, there are still many people who believe that clinical trials may assure safety of the device. Clinical trials are effective to evaluate a new medical device with no established procedures along with the method for use. However, to evaluate a device, only part of which has novelty, "clinical evaluation" alone would be sufficient in most cases.

(2) Hollowing out of clinical trials of medical devices

Medical devices whose effectiveness and safety can only be evaluated in clinical trials need to undergo clinical trials. There is so-called "hollowing out of clinical trials," a phenomenon where a Japanese company developing such an extremely novel medical device initiates a clinical trial in Europe, followed by another in the U.S. and, recently, in Asian emerging countries, and finally in Japan. The first clinical trial of a small bowel capsule endoscope was conducted in Europe and the product was launched in October 2005, followed by the launch in the U.S. market in May 2007. However, it was September 2008 when it was finally approved in Japan[12] after undergoing a clinical trial in Japan. The application for approval of an implantable ventricular-assist device was submitted in December 2009 and it was in March 2011 when the device was approved, three years behind the market launch in Europe. Recently, it has been reported[13] that a bioabsorbable stent developed by a Japanese company was launched in the European market in 2009 but that the company has no prospects at all of launching the product in Japan.

There should be an environment where companies, no matter how small in scale they are, that develop new medical devices made in Japan can plan and conduct more clinical trials.

Causes of the "hollowing out of domestic clinical trials" are the difficulty in ensuring the time, cost

[12] This product was selected as an designated product by the committee for early introduction of medical devices of high needs after filing.

[13] According to the report, although the bioabsorbable stent that was put into practical use for the first time in the world by Kyoto Medical Planning Co., Ltd was launched in European markets in 2009 and is being prepared for sales in South Korea, it has been impossible to expect its marketing in Japan due to the high costs of conducting clinical trials and the long period required to obtain approval (Nikkei Sangyo Shimbun dated November 29, 2010).

and resources required conducting clinical trials and the lack of predictability in time required for approval review and reimbursement. Efforts are made to achieve satisfactory results first in foreign countries where the time to market is shorter so that companies can reduce the scale of domestic clinical trials and make effective use of overseas data to receive favorable review by the regulatory authority in Japan. For these reasons, in developing a device for highly rare disease, Japan is the first to be removed from a list of candidate countries for its development.

(3) Issues regarding environment for clinical trials of medical devices in Japan

To conduct a clinical trial, a dedicated organization and staff are required. Unlike drugs, medical devices are required to undergo clinical trials every several years and there are few companies that can internally afford a dedicated team. Medical facilities participating in clinical trials of medical devices are divided into two groups: those constantly involved in clinical trials of medical devices, such as cardiovascular specialized hospitals, and the others.

Less conduct of clinical trials often result in a fewer number of trained internal monitors and CRCs (clinical research coordinators) at facilities. In addition, while drugs can be managed by clinical trial management centers, medical devices cannot be managed because of difficulties specific to devices, such as dispensing of devices and their physical size. For these reasons, there are no other ways but to outsource clinical trial activities to CROs (contract research organizations) and SMOs (site management organizations), which is a contributing factor to soaring costs for clinical trials.

In addition, under the current circumstances, the National Health Insurance reimbursements do not always reflect the development costs even if a clinical trial has been conducted. The life cycle of medical devices lasts a few years, which is extremely shorter than that of drugs. Therefore, if the development costs could not be reflected to reimbursements, the return of investment will not be favorable, which discourages business owners to adopt new technology and equipment. This is the major reason that makes it difficult to launch and expand new business ventures of medical devices in Japan.

Table 2 shows the summary of the aforementioned issues and other issues that hamper the conduct of clinical trials of medical devices.

Table 2: Issues regarding medical device clinical trials[14]

Category	Issues
Clinical settings	Dispersions of enrollments: • The number of hospitals is relatively high but there are only a small number of specialized hospitals, resulting in the tendency of dispersion of study subjects. Time availability of doctors: • Doctors in Japan are extremely busy. Unlike clinical trials of drugs, doctors are not allowed to have research nurses provide treatment and surgery in clinical trials of medical devices, which limits their participation in a clinical trial in addition to their busy daily practice. • Too much dependence on monitors, too many visits • No career credit for their participation in clinical trials, leading to low motivation • No incentives for study sites to participate Clinical settings: • Less experience in clinical trials of medical devices (same with companies) • Not possible for the clinical trial management center to manage devices due to dispensing of devices and their physical size.
General public	Loss of opportunities to participate in clinical trials: •Patients may have delayed or missed opportunities for accessing cutting-edge medical devices because of delayed or no clinical trials in Japan.
Costs	High-cost structure: •Considering the actual circumstances in clinical sites, it may be essential to use CROs and SMOs. However, due to the high costs for using them, the expected benefits may not justify the investment required. •For relatively small-scale medical devices companies and venture companies, it is extremely difficult to maintain clinical development personnel for a medical device clinical trial that is conducted only once or none in several years.

(4) No recognition of clinical research under the law

The development process of medical devices is different from that of pharmaceutical products. In developing medical devices, it is sometimes required to conduct a performance test in human subjects. However, the current Pharmaceutical Affairs Law only provide the definitions and regulations related to clinical trials for obtaining approvals but not related to those for other purposes. This makes it difficult [for companies] to use unapproved medical devices for performance tests for the aforementioned purpose.

2) Proposals for the aforementioned issues

(1) Departure from the supremacy of clinical trials by promoting clinical evaluation methods

i. In applying for approval of a novel device, firstly, the feasibility should be thoroughly investigated whether it is feasible to evaluate the effectiveness and safety of the device based on previous results from clinical trials (experience) and performance tests, or other non-clinical studies, or literature.

ii. If the investigation proves that the clinical effectiveness and safety of the device cannot be evaluated only based on performance, animal and other non-clinical study results or existing literature, clinical trials will become necessary. In such cases, a “clinical evaluation” method

[14] Modified from the original article by Kodama J. Issues Surrounding the Development and Approval Processes of Medical Devices [in Japanese]. Journal of Health Care and Society. 2009;Vol.19 (1):51-71.

should be applied to clinical trial to limit the number of subjects and focus on objectives.

(2) Elimination of the hollowing out of clinical trials

i. Implementation of approval application and review by applying “clinical evaluation” methods

ii. Achievement of the performance goals in the “Action Program for Acceleration of Medical Devices Review Process” established by the Ministry of Health, Labor and Welfare in order to make the time required for approval review predictable.

iii. In the case where a domestic clinical trial is required, the clinical trial notification may be submitted almost concurrently with the application for approval and interim reports may be provided during the process of the review of the application.

iv. As a method for quick market access, unnecessary verification tests (pivotal studies) should be replaced by a postmarketing study.

v. For medical devices for a highly rare disease and/or those with high medical needs, review should be conducted based on “safety and probable benefits” in reference to the HDE (Humanitarian Device Exemption) system in the United States.

vi. Grants for facilities participating in clinical trials (incentives for clinical study sites)

vii. National efforts to raise public awareness about clinical trials

viii. Setting of National Health Insurance reimbursement codes by taking into account the rarity of disease and medical needs

(3) Promotion of clinical trials of medical devices (improvement of environment)

i. National efforts to establish clinical trial sites dedicated to highly specialized medical devices

ii. Awarding of academic degrees to clinicians publishing research papers on clinical trials (incentive to investigators)

iii. Grants to facilities participating in clinical trials (incentive to clinical sites)

iv. National efforts to raise public awareness about clinical trials

v. Clarification of the scope of monitor’s responsibilities and revision of the GCP related to reliability assurance to comply with international harmonization

vi. Coverage of the expenses for medical devices by insurance (compensated clinical trial)

vii. Reimbursement system for recovering costs for clinical trials

(4) Clinical research

A system to allow for conducting clinical research (clinical trial) requested by a company should be established in order to use its results as material for clinical evaluation.

The current issues regarding clinical trials of medical devices and proposals to solve the aforementioned issues are summarized in **Figure 6**:

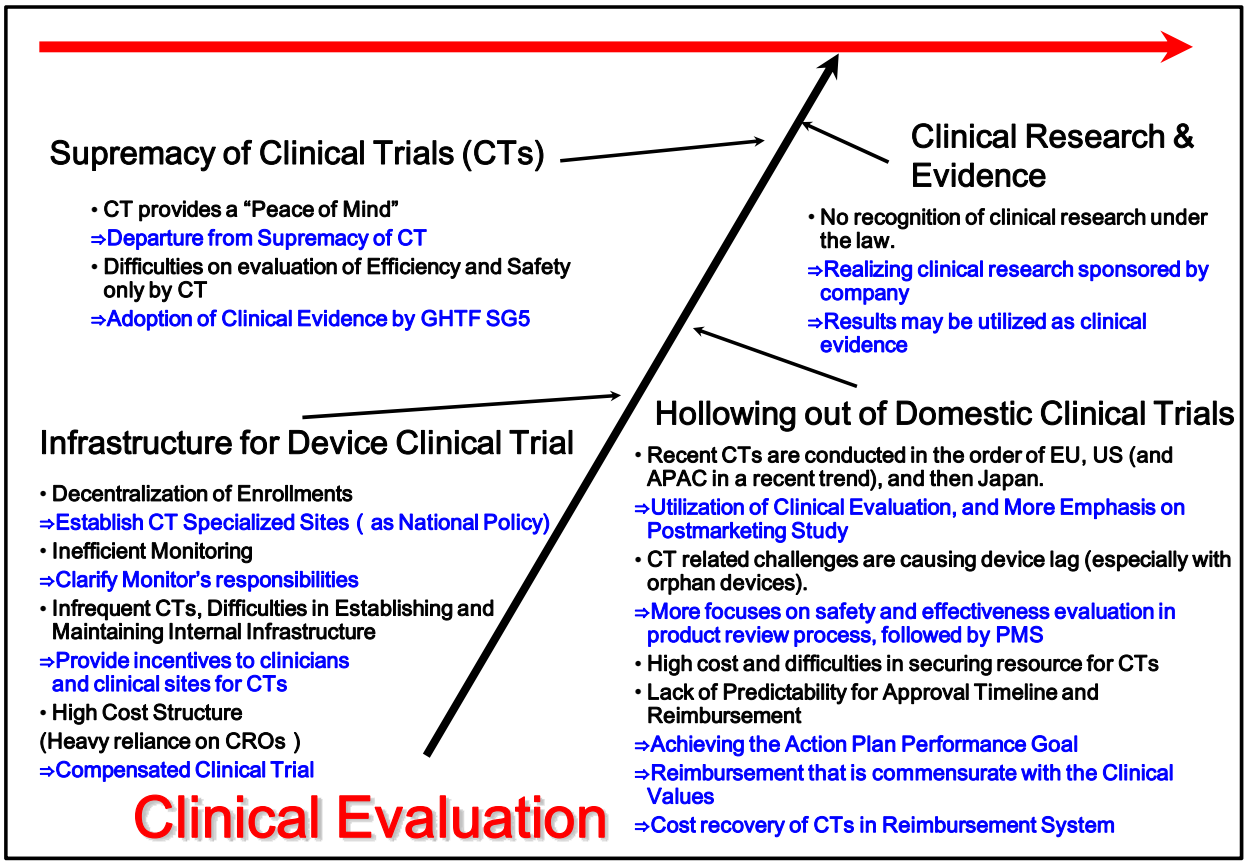


Figure 6: Issues and proposals regarding clinical trials of medical devices

Summary of proposals: One of the major factors that affect the device lag or device gap is clinical trials. It is essential to evaluate the efficacy of drugs in clinical trials. In contrast, the effectiveness of medical devices can, in most cases, be evaluated using other methods than clinical trials. In order not to lag behind the constantly evolving development of medical devices and, at the same time, in order to use devices safely, it is important to gather safety information carefully while focusing efforts on standardizing methods and skills to use medical devices that were introduced with a short time to market. One of the effective methods to achieve this goal is "clinical evaluation," which is based on all kinds of information that can be gathered, such as previous results from clinical trials, clinical research, clinical experience, non-clinical studies, and literature. The CE marking system in EU is one of successful examples for such approach.

It is also the fact that it is desirable to evaluate medical devices in clinical trials if there are no established methods for use. Clinical trials are indispensable for clinical evaluation of such devices. To address this, it is also important for the government to provide improved environment for clinical trials in order to prevent the hollowing out of domestic clinical trials.

5. Premarket Review

The 2005 revision of the Pharmaceutical Affairs Law introduced assessment of the Summary of Technical Document (STED), a product of the GHTF discussions, and conformity with the Essential Principles (EP), a system promoted by the EU. The introduction of this assessment method made the content of design verification subject to review. This change introduced the concept of ISO 13485 and efforts have been made to meet international standards.

Despite this move, there are requirements for approval/certification (called *shonin*/*ninsho* requirements in Japanese) to provide specific, detailed information on medical device raw materials, shape and other features. These requirements are unique to Japan. Unlike with drugs, medical devices must be operated by physicians or other healthcare professionals, so improvements to the safety, quality, shape and function of the devices must be based on postmarketing quality information provided by customers, including complaints from customers and Medical Device Reporting (MDR). However, medical device manufacturers are required to provide detailed information on the specific raw materials, shape and other characteristics in the approval/certification submission, just as with drugs that are reviewed on the premise that the active ingredient will not change. This system means that every time a quality improvement is made, an additional premarket review by PMDA or a Recognized Certification Body is required. This not only increases industry workloads and review fees, but results in prolonging the time for approval/certification, preventing appropriate improvements from reaching the market in a timely manner.

1) Problems

(1) Device lag/device gap

A survey[1)] involving companies in Japan, the U.S. and EU was conducted regarding the launch timing of products developed in Japan, the U.S. and EU. The majority of the surveyed devices were introduced in Japan last. Even some of the products that were originally developed in Japan were launched first in the U.S. and/or EU (**Table 3**). For example, for products that were introduced in the U.S. first, followed by the EU, and then Japan (12.3%), the mean approval lag between Japan and the U.S. was 2,005 days or about 5.5 years.

Table 3: Comparison of time to market launch between Japan, the U.S and E.U.[15]

Order of approval/license/certification (in the order from the first to the third)	Sample size			Gaps of approval/license/certification (mean gap in days)		
	Country of origin		Percentage of total	1st to 2nd	2nd to 3rd	1st to 3rd
	Overseas	Japan				
US-Japan-EU	4	-	0.6%	416 days	157 days	573 days
US-EU-Japan	85	-	12.3%	533 days	1,472 days	2,005 days
EU-US-Japan	67	1	9.8%	524 days	1,337 days	1,861 days
EU-Japan-US	1	-	0.1%	218 days	62 days	280 days
US/EU (simultaneously) - Japan	8	-	1.2%	1,173 days	NA	1,173 days
US-Japan	67	-	9.7%	1,699 days	NA	1,699 days
EU-Japan	55	9	9.3%	1,086 days	NA	1,086 days
Japan	188	196	55.6%	NA	NA	NA

Note: Devices on which no information is available either in the U.S. or in EU are included in the boxes for Japan at the bottom of the table. Therefore, the numbers in these boxes are not necessarily those distributed in Japan alone. If the date of the year, month, and day of an approval/license/certification was missing, it was assumed that it was obtained on the first day of the month. If the year alone was known, the product was included in the sample size but excluded from the analysis of mean lags. If there were more than one date, the oldest was used.

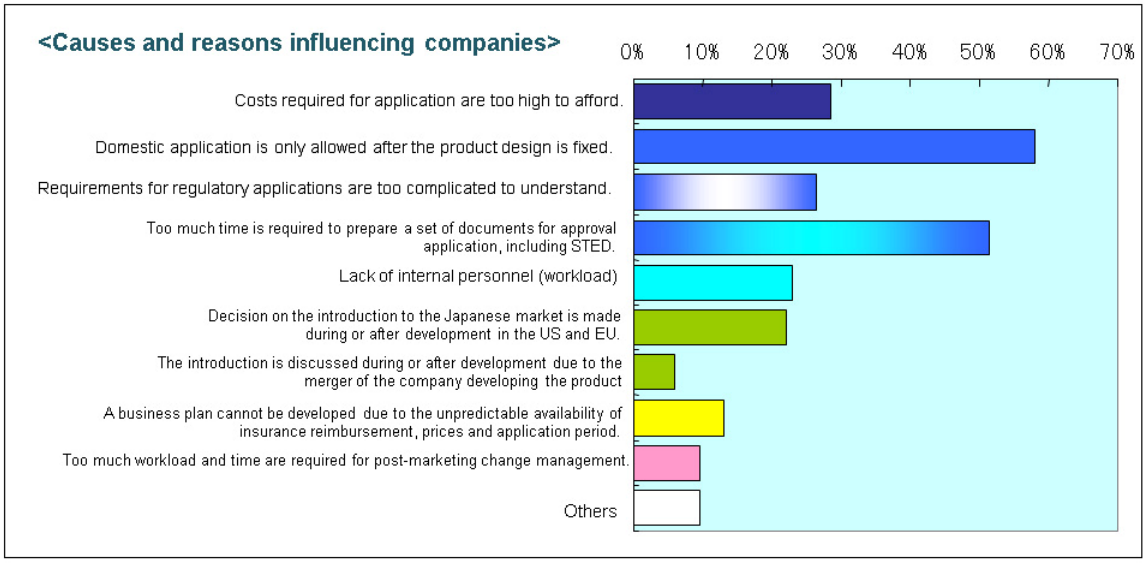
Device lags can be divided between submittal lag (the delay in submission for approval in Japan compared with other countries) and approval lag (the difference between Japan and other countries in the period from application to approval). A survey[16] on factors for these device lags was undertaken in 200 companies developing their businesses both in Japan and abroad (**Figure 7**), focusing on the decision-making process for the medical device introduction and on submittal lag.

Factors leading to delay in introducing medical devices include the high costs associated with approval applications, issues with the National Health Insurance system after market launch (price, timing, recalculation, etc.), and the long time required before marketing and unpredictable approval timing making it difficult for companies to develop business plans.

Before applying for approval, companies must obtain information specifically for Japan and data from non-clinical studies, and sometimes from clinical trials, that are also specific to Japan. These reasons mean that, even after deciding to introduce a product, a company may still experience a submittal lag.

[15] 2011 Time Clock Survey: AMDD, The Japan Federation of Medical Devices Associations (JFMDA), EBC internal document

[16] 2011 Submittal Lag Survey: AMDD, The Japan Federation of Medical Devices Associations (JFMDA), EBC internal document; Percentages reflect those who responded “influenced” among 200 responding companies (top 10 items)



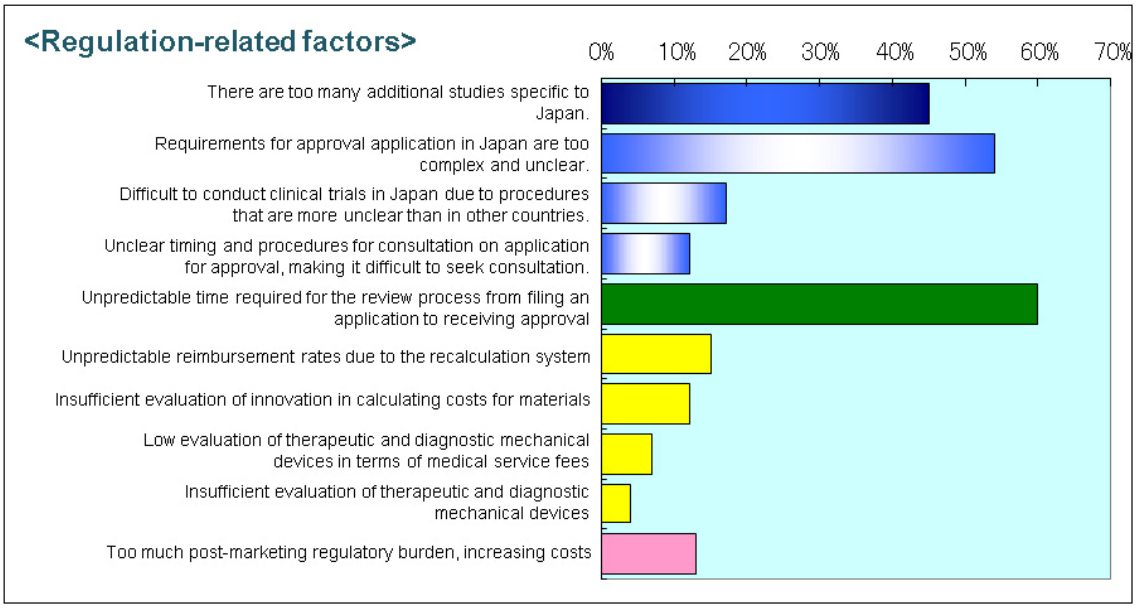


Figure 7: Factors affecting decision-making on the introduction to Japan (company-based and regulation-based) [17]

[17] 2011 Submittal Lag Survey: AMDD, The Japan Federation of Medical Devices Associations (JFMDA), EBC internal document; Percentages reflect those who responded "influenced" among 200 responding companies (top 10 items)

In addition to these factors, there are concerns over post-approval requirements (submission requirements for post-approval changes, user education and training, research on product usage and performance, traceability of biological materials, etc.) which cause companies to give up on introducing devices in Japan. This tendency is most remarkable in medical devices for pediatric use and only a small number of patients, and for devices using absorbable materials and biological materials for which requirements are more stringent in Japan than in other countries. The aforementioned lack of device introduction is called a device gap. While the reasons differ between cases, about a half of medical devices that have been approved in the U.S and/or Europe are never introduced in Japan. (**Figure 8**)

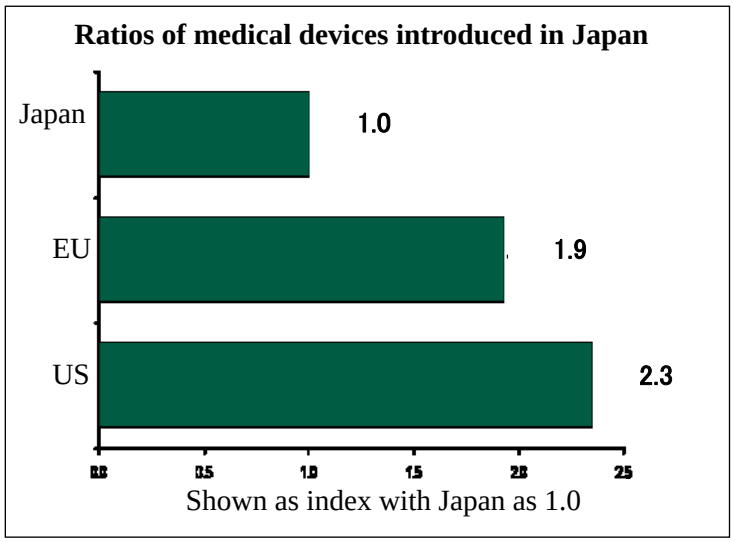


Figure 8: Comparison of device gap between Japan, EU and the U.S.[18]

(2) Workload on document preparation for submission

One of the reasons contributing to device lag is the workload required for the entire process from preparation for regulatory application to filing of the application. In the U.S. and EU, the result report from design verification tests prepared during the design control process can be used as an appendix to the application documents submitted to the regulatory authority. In Japan, however, the review concept is based on identifying the medical device by its raw materials (similar to drugs), so the applicant is required to provide information more detailed than the manufacturer actually controls on-site.

In addition, some test data unnecessary in foreign countries (material deterioration testing of products sterilized with radiation at the maximum dose, real-time stability testing, etc.) are required in Japan. This requires additional time, greater workloads and increased costs, and is a major factor contributing to the submittal lag (**Figure 9**).

[18] 2011 Time Clock Survey: AMDD, The Japan Federation of Medical Devices Associations (JFMDA), EBC internal document

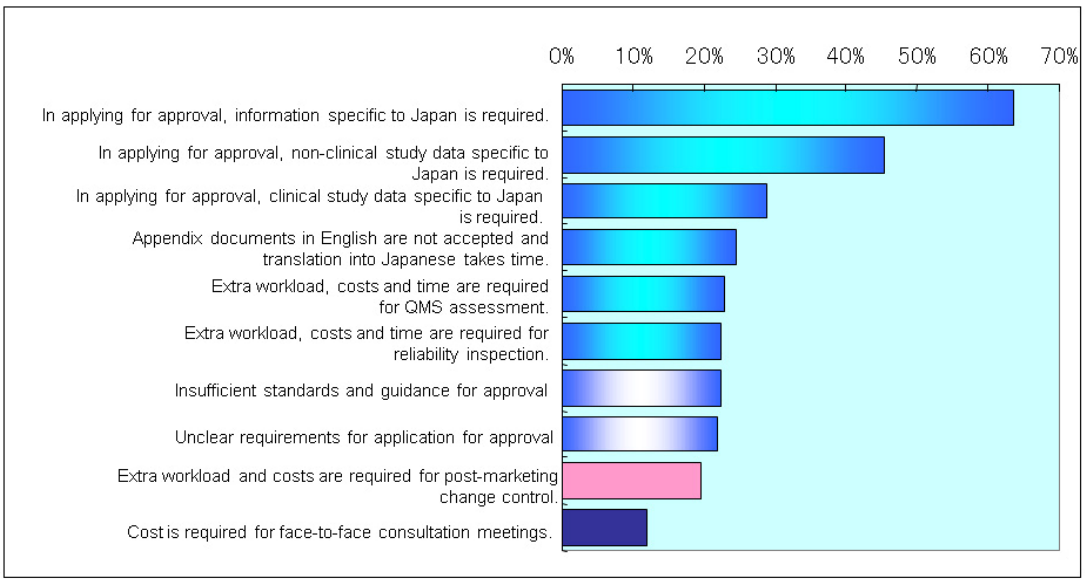


Figure 9: Regulatory factors affecting submittal lag in Japan[19]

(3) *Shonin* requirements and change control

As described in (2), extremely detailed information is required for approval submissions. Even minor internal changes in manufacturing and quality control for which no official approval is required in other countries require a partial amendment application for post-approval change in Japan.

Drugs are defined by chemical substances and their usage is defined by dosage and administration alone, so information on proper use based on postmarketing information on adverse drug reactions can serve measure improvement towards safer and more effective use for drugs. On the other hand, medical devices are composed of a variety of materials and technologies, and must be operated by physicians or other healthcare professionals. The premarket design and development process for devices is based on constant review of postmarket information to drive device improvements, but the processes required by current regulations prevents implementation of workflows that would achieve appropriate and timely improvements (**Table 4**).

[19] 2011 Submittal Lag Survey: AMDD, The Japan Federation of Medical Devices Associations (JFMDA), EBC internal document; The percentages of those responding “influenced” among 200 responding companies (top 10 items)

Table 4: Differences between medical devices and drugs [modified from 20]

	Medical devices	Drugs
Market size	About ¥2.2 trillion	About ¥8.37 trillion (drug price)
Difference in numbers	15,000 products (300,000 kinds)	17,000 products
Difference in materials	Composed of a variety of materials (resins, metals, etc.) and electronics	Natural substances/chemical substances, etc.
Development concept	Innovation through novel developments and improvements in clinical settings	Innovation through novel development in laboratories
Effects	A wide variety of effects (physical effects, electrical effects, etc.)	Mainly chemical effects
Usage	Need to learn method of use	Dosage and administration
Maintenance	Maintenance required	No specific requirements
Professional education	No education in a specific field required	Department of Pharmacology
Hospital staff	Medical device management center Clinical engineer	Pharmaceutical Department Pharmacist
Postmarketing surveillance	Gathering information on complaints, defects and malfunctions	Gathering information on adverse drug reactions
Postmarketing improvement activity	Improvements to manufacturing and quality control Improvements to make products easier to use Provision of information for proper use	Provision of information for proper use

Medical devices are identified according to raw materials used, just like drugs, so every time an improvement is made, submission of either a new or partial amendment application for a post-approval change is required. Since reviews are normally required for each product, if the same change is made in more than one product (for example, a change in the sterilization method across multiple products), reviews are required for every submission, requiring review fees and change control for each product.

The Pharmaceutical Affairs Law revision from 2005 introduced a system of minor change notification, but this system is only applied when it is clear that change does not have any impact on quality, efficacy and safety. If there is any concern that the change may affect quality, efficacy and safety, the manufacturer is then required to file a partial amendment application for the post-approval change. Even with this additional regulatory category, the scope of “minor change” is still very limited. Even though many manufacturers of medical devices continuously work to improve the quality, effectiveness and safety of their products, the Japanese regulations hamper their efforts improving medical devices.

Even for medical devices classified as Class I (general controls) with the lowest risk, a “notification” containing information similar to that required for an approval/certification application is required. For example, a notification is required even for small steel instruments such as forceps that are manufactured in response to a surgeon's specific order. Since the notification requires detailed device information, if changes are frequently made the manufacturer must undergo the cumbersome process of submitting a notification every time a change is made.

[20] AMDD internal document

(4) Requirements on raw materials

There are many medical devices made of general purpose plastics such as polyethylene and silicone resins, yet, detailed data, including a list of components that comprise plastics, is required for these devices. Manufacturers usually add and/or change the suppliers from which they purchase raw materials so that they can maintain more than one supplier to ensure stable supply. Japan's regulations require a partial amendment application for post-approval change every time they add or change suppliers because the raw material details differ from supplier to supplier.

It is also required, in principle, to perform real-time stability testing every time the raw material is changed. For example, if the manufacturer intends to set a shelf life of two years, a two-year real-time test is required. While it is allowed to rationally set a shelf life based on results from accelerated aging and other tests in foreign countries, the use of an accelerated aging test is limited to certain cases in Japan, forcing manufacturers to carry a large amount of inventory of pre-change products to maintain steady supply until the post-approval change is approved.

(5) Regulations for biological products

In Japan, regulations for products using biological materials such as tissue valves, heparin coatings and casein are more stringent than those in foreign countries. For example, manufacturing a product using inactivated tissue is very difficult to secure suppliers of biological materials in foreign countries that comply with the Japanese regulations since there are Japan-specific regulations for breeding management of donor animals and retention of records. In some cases, it becomes necessary to develop a product unique to Japan in addition to the one distributed globally. This increases costs and makes global inventory management impossible, thereby raising concerns regarding stable supplies to Japanese customers.

Many companies give up introducing new biological products due to these regulations. The number of companies dealing with biological materials has decreased since the introduction of the regulations, posing a barrier to the introduction of new products. This has affected the introduction of products that take advantage of the benefits of anticoagulant properties of biological materials (e.g. tissue valves, heparin-coated catheters). When the regulations were adopted, there were 31 companies that possessed approved medical devices using heparin (catheters, artificial heart and lung circuit, etc.); this has been declined to 18 (as of September 30, 2010). The approximately 10 companies with approved cell-tissue-derived medical devices (tissue valves, biological patches, etc.), was once declined to two and later increased to four (as of April 8, 2011).

(6) Issues with *Ninsho* standards

The third-party certification system, newly adopted in the revised Pharmaceutical Affairs Law implemented in 2005, has been used steadily. However, there are many inherent issues in developing and implementing *ninsho* standards.

The first issue is that only JIS (Japanese Industrial Standard) standards are referred to in the notifications on certification standards, but it takes several years to incorporate changes made to original IEC or ISO standards into JIS standards. This is true even for JIS standards unique to Japan. Even though interim measures can be taken, fundamental revision is necessary, which takes several years. This system prevents JIS standards from reflecting revisions of the international standards that ensure effectiveness and safety in a timely manner. This is a serious problem.

The second issue is that it is unreasonable to include performance specifications or measuring methods in Article 6 (Efficacy of medical devices) of the Essential Principles Conformity Checklist. This is not in line with the original intent that "the intended efficacy of a medical device must outweigh the foreseeable risks." This implementation conflicts with the intent of the Article requiring risk benefit analysis with the market value and clinical efficacy.

2) Proposals regarding issues regarding premarket review of medical devices

(1) Device lag/device gap

i. The least burdensome concept should be introduced; reviewers should not seek submission of materials extraneous to the review. PMDA should provide advice to facilitate the development of medical devices and establish a system that provides applicants and consulting parties with information on effective verification methods according to the characteristics of each medical device. There also needs to be ongoing verification that reviews are performed in this manner.

ii. Reviews should be based on evidence of safety and probable benefits, particularly for devices for rare diseases and for pediatric use. There needs to be a flexible system with reviews focused on safety evaluation and allowing existing literature for effectiveness evaluation, by considering the FDA's Humanitarian Device Exemption (HDE). In addition, the adoption of a system that allows manufacturers to recover some of the investment from the development and investment period should be considered. (See "4. Clinical trials")

iii. An incentive mechanism is needed for promoting development, such as National Health Insurance reimbursement that reflects clinical value. In addition, an environment that facilitates business planning should be made through improving the postmarketing recalculation system, for example, by abolishing the Foreign Average Pricing (FAP) system.

iv. For products which academic societies request approval, the Study Group on Early Introduction of Medical Devices with High Medical Needs discusses the appropriateness of early introduction. Current segmented process must be replaced with a seamless and integrated system covering the initial discussions, the review process and health insurance decisions, as shown in **Figure 10**.

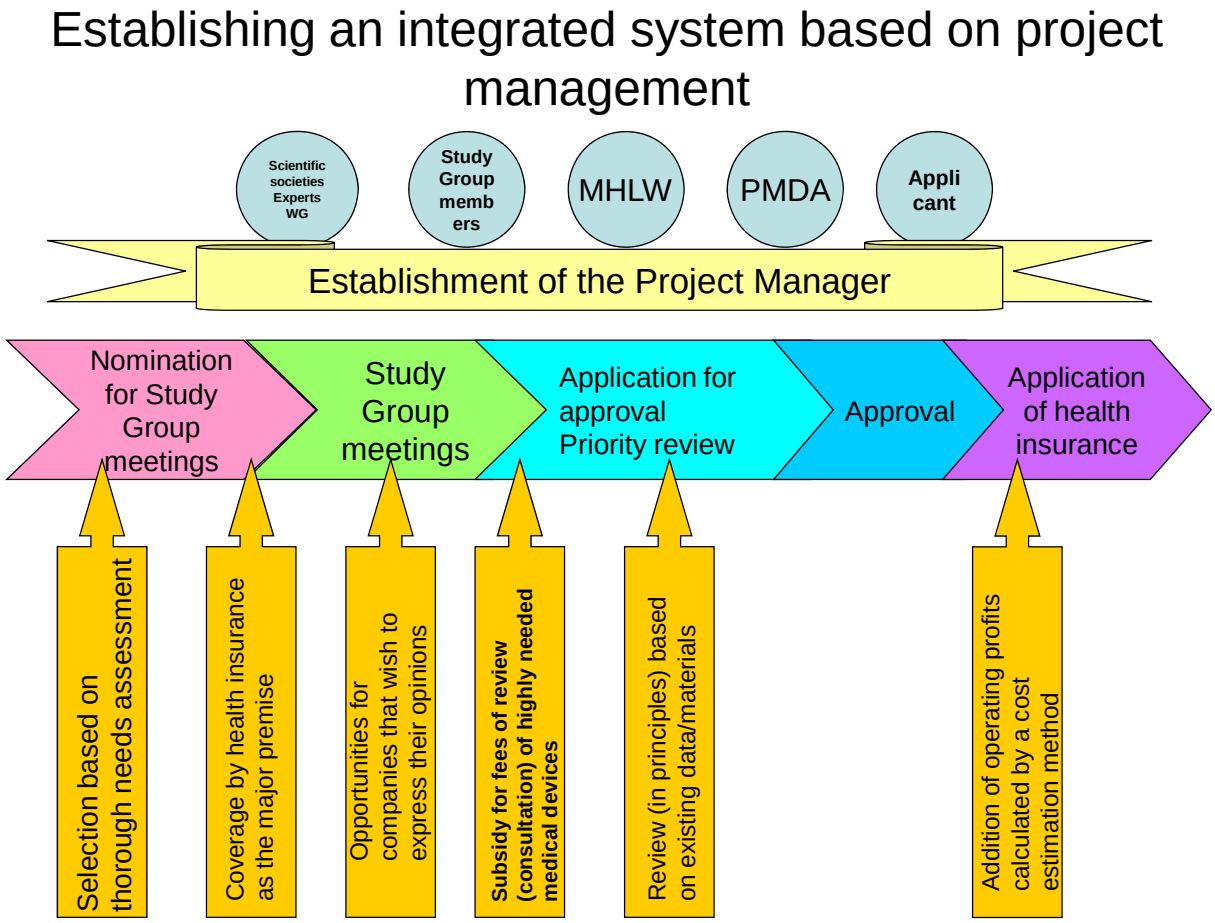


Figure 10: Proposed review system to facilitate early introduction of medical devices with high medical needs

(Source: Materials submitted by AMDD at The 7th Periodic Regulatory Round-table Meeting on medical device regulations)

v. To accelerate review of medical devices, product review and QMS conformity assessment should be outsourced as much as possible to Recognized Certification Bodies and third-party certification organizations [such as Notified Bodies] so that PMDA can focus into product review of highest risk (Class IV) devices and new medical devices and to QMS conformity assessment (corresponding to FDA's PMA review) in order to utilize its limited resources effectively. For example, by designating medical devices in Class III as Controlled Medical Devices like Class II devices, it will be possible to change those device reviews from "approval by PMDA based on approval standards" to "product review by a Recognized Certification Bodies." In the EU where the classification of medical devices is consistent with Japanese classification, only medical devices with the highest risk are required to undergo document review on a product-by-product basis; other devices are reviewed by the rational method of grouping products that share a common design philosophy ("group certification[21]").

[21] Health Labor Sciences Research "Research regarding the third party certification system for medical devices in Class II" December 2008-March 2010.

(2) Workload on document preparation for submission

i. Data accepted through review in the U.S. and EU and data obtained by a commonly recognized test method should be accepted without requiring additional data specific to Japan.

ii. Product specific QMS inspection and reliability inspection are (with the exception of clinical trials) systems unique to Japan. The product specific QMS inspection should be replaced by the site specific QMS inspection. By confirming that products are to be manufactured at a manufacturing site that comply with the ISO 13485 standard, the burden imposed within the approval review process could be reduced (See "2. Quality Management System (QMS).")

iii. Even if data were obtained at the manufacturing site whose compliance to the design control requirements of the QMS has already been verified, the data are required to undergo reliability inspection in addition to QMS inspection, resulting in redundant verification. If data have been submitted by an organization where the design control system has been verified to be compliant with the standard, reliability inspections other than GCP and GLP should be exempted.

(3) *Shonin* requirements and change control

i. Medical devices are required to demonstrate their performance when used for their intended purposes. Therefore, unlike drugs, which are reviewed mainly based on chemical substances and ingredients, medical devices should be reviewed mainly based on their function and effectiveness.

ii. The current approval system for medical devices is based on the system [optimized] for drugs, which is based on the concept of product-by-product review mainly based on trade names and ingredients. Our proposal is to abolish this concept and establish a mechanism that allows manufacturers to receive approval according to technical background and principle of medical devices. For example, for low risk products, something like the CE mark system applied in Europe would be ideal: the manufacturer would receive the CE mark for a group of products (for example, under a generic name), and later add derivative products to the group through self-declaration. For high risk products, just as with the FDA's PMA, approval would be given under the name of "PTCA catheter manufactured by ABC Company," and products subsequently developed through a series of improvements and new functions added to the originally approved one will be included in the same file. This system would allow verification and review to focus on the differences caused by improvement in an integrated manner. In addition, approval and review of a change affecting more than one product could be submitted together in one application, improving the efficiency.

iii. For approval review, the degree of compliance of the manufacturing site with the QMS requirements is assessed. This requires descriptions of the manufacturing site in terms of QMS alone, address and other information are not necessary. (See "2. Quality Management System (QMS).")

iv. Review of changes made to a product should be required only when it is confirmed in verification conducted by the applicant that the quality and safety of the improved product are different from those of the originally developed product. Otherwise, the applicant should only be required to submit a Minor Change Notification. The provisions of Article 47 of the current enforcement regulations are based on the assumption that they are applicable to drugs. Therefore, as shown in **Table 5**, provisions dedicated to medical devices should be provided separately.

Table 5: Proposal regarding the scope of minor change

Article 47 of the current enforcement regulations	Proposal of provisions dedicated to medical devices
Minor changes are changes other than those listed below: (1) Change in the manufacturing method of the product that affects its nature, properties, performance and safety (2) Deletion of items listed in the sections of the specifications and study methods, and change in the specifications (3) Change in inactivation or eradication methods for pathogenic agents (4) Addition, change or deletion of descriptions of administration or dosage, or indications or efficacy (5) In addition to the changes listed above, any change that could possibly affect the quality, efficacy and safety of the product	Minor changes are changes other than those listed below: (1) Addition, change or deletion of the intended use (2) Significant change in product design (3) Change that could impair significantly the quality, effectiveness and safety of the product

(4) Requirements on raw materials

Reconsideration of the positioning and content of the approval letter for reviews focusing on whether or not the design and development were appropriate and reasonable are needed. For medical devices, it is important to make appropriate and timely improvements based on postmarketing information gathered from the market and the manufacturing process. This activity corresponds to change control and design control processes of a quality management system (ISO 13485). These changes associated with improvement should be controlled within the framework of internal QMS activities in the postmarketing setting. In this context, the information on specifications of incoming parts, in-process test methods, and acceptance criteria should not be included. In particular, the descriptions of raw materials should be limited at generic name level, as in the U.S. and E.U. and any information that is not controlled by the manufacturing site should not be required.

(5) Regulation for biological products

There is no room for argument about the necessity of certain regulations for biological products. However, excessive regulations will make it difficult [for companies] to introduce products that are used in foreign countries and cause negative impact to patients' benefits. Therefore, we consider it necessary to review the standards for biological materials and notifications regarding viral inactivation to make them consistent with regulations of other countries. In particular, because casein is not included in regulations for viral inactivation in foreign countries and is prepared by alkali treatment and heat treatment, it is possible to recognize casein as a highly purified product. And for heparin, information on the viral inactivation process is considered as highly proprietary to heparin manufacturers, so it is very difficult for them to disclose the information. This appears to be the reason that many companies have withdrawn from the development of heparin and given up market entry.

For viral inactivation, more flexible measures should be taken, for example, allowing a written statement by the supplier as a substitute.

The figure below shows our proposals for a review of regulations regarding biological materials at the time point seven years after the introduction of the regulations (**Figure 11**).

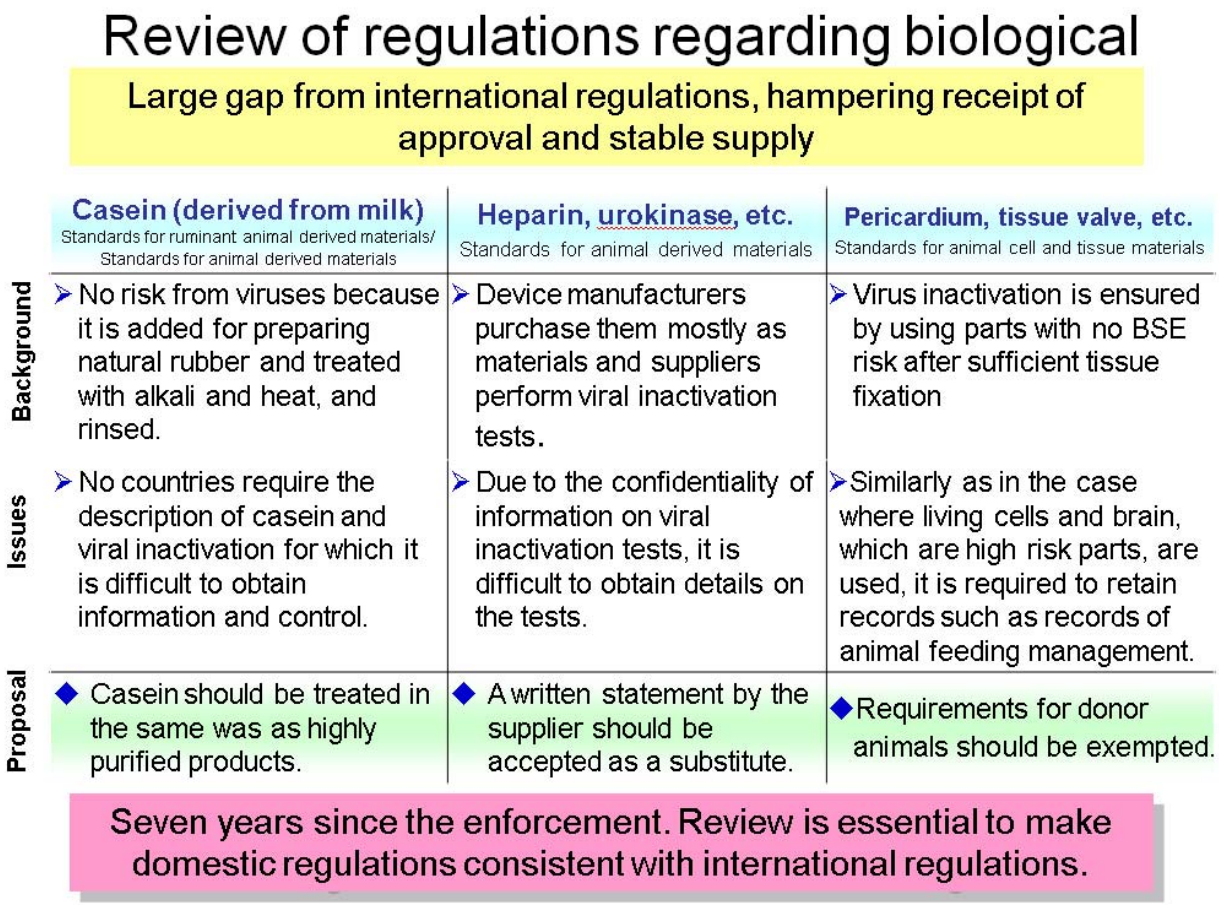


Figure 11: Proposals regarding regulations related to biological materials
（Source: Materials submitted at the 8th regular round-table meeting on regulations for medical devices in 2010）

(6) Issues for *Ninsho* standards

i. If a JIS standard is mandated for certification (*Ninsho*) by Public Announcement (*Kokuji*), devices that do not meet all the specifications in the standard will be classified as deviated products under a strict interpretation. “Standard” typically provides general specifications for ensuring quality and safety and their voluntary application is considered appropriate. Standards for certification should only include “Nomenclature” and “Intended use and Efficacy or Effect,” and the use of the Medical Devices Essential Principles Checklist published as a notification should be used, should be sufficient in its present form. “Effects and efficacy” should be used when drugs are evaluated and “*Seino*[22]” should be used to evaluate medical devices.

[22] In the United States, "efficacy" is used for drugs and "effectiveness" is used as its counterpart for medical devices. Since there is no Japanese word to accurately translate effectiveness while discriminating between "efficacy" and "effectiveness," the original Japanese version of this articles uses “*seino*” throughout as a translation of "effectiveness."

ii. At present, Article 6 of Japanese Essential Principals (EP) "Efficacy of medical devices" requires performance descriptions. However, performance descriptions are included in Article 16 "Performance evaluation," and it is redundant. This was adopted as a temporary measure when Article 7 and subsequent articles in Chapter 2 were not temporarily applied when the revised Pharmaceutical Affairs Law was enacted in 2005. Therefore, the effectiveness items should be removed from Article 6.

The current issues regarding premarket review of medical devices and proposals to solve the issues described above are summarized in **Figure 12**:

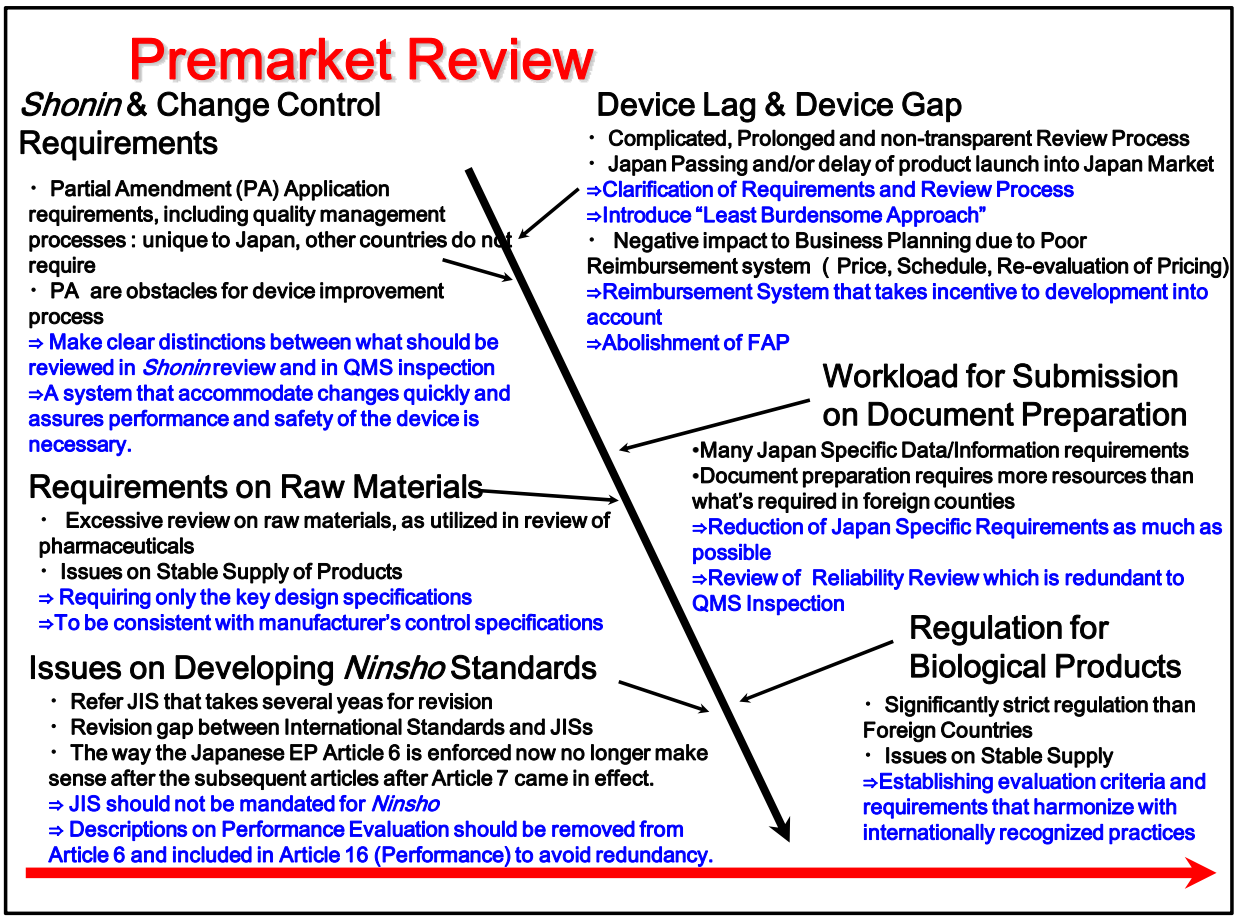


Figure 12: Issues and proposals regarding premarket review of medical devices

Summary of proposals: Premarket document reviews and the postmarket information controlled internally through QMS should be managed separately. Review methods and systems specific to medical devices should be established to promptly reflect changes made for improvement and to reasonably ensure safety and effectiveness.

6. Postmarket Safety Management (GVP: Good Vigilance Practice)

The current Pharmaceutical Affairs Law requires MAHs to gather, analyze and evaluate postmarket safety information on medical devices on their own responsibility and, as needed, take measures to secure safety. This leads not only to secure safety but also, as a result, to allow continuous improvement of products after marketing.

To achieve continuous improvement of medical devices, there is a continuous process called PDCA or Plan-Do-Check-Action Cycle: Plan (development and product design); Do (manufacturing, sales and use); Check (gathering, analysis and evaluation of postmarket information on quality and safety); Action (activity to improve design, manufacturing, sales and maintenance based on evaluation). The use of the PDCA cycle in activities required in postmarket safety management to gather, evaluate and analyze postmarket information and to provide feedback is an effective way to achieve the main objective to provide users with proper use information to ensure the safe use of products. Since the PDCA cycle concurrently functions as a power source to promote product improvement, it is extremely important to use the cycle effectively and efficiently in order to develop a better product in a shorter period of time (**Figure 13**).

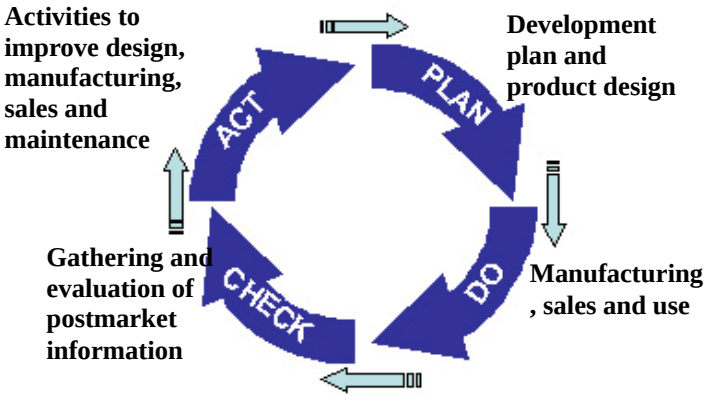


Figure 13: PDCA Cycle

Information obtained in the postmarket phase is often derived from adverse events and user complaints. The subsequent process consists of the part where information is gathered and analyzed (corresponding to “C”) and, after gathering and analyzing as much information as possible to identify causes, the part where measures to prevent recurrence are taken (corresponding to “A”) will follow. Depending on the cause, the safety control method currently applied may be enhanced or the product concerned may be removed from the market. The regulatory authorities require the submission of MDR and recall reports, which cannot be prepared only by the supplier of the product but will inevitably require full cooperation from medical facilities that use the product.

This series of activities is “postmarket safety management activities” and it is required by the GVP Ordinance to implement these activities as a system. These activities, which are conducted on the initiative of the MAH that assumes the primary responsibility for the product, have an inextricable relationship with the GQP Ordinance. For this reason, it is rational to consolidate these two Ordinances.

1) Issues regarding postmarket safety management of medical devices

(1) Recall and field action systems

Drugs are metabolized in a certain period of time. Therefore, recall of drugs to secure safety mainly means to “remove drugs from the market in order not to be used. As for medical devices, due to a great diversity of purposes of recall, ranging from repairs of installed large devices to monitoring of patients implanted with a device, the two terms and concepts, recall and field action, are applied. Under the current system, there are following issues:

i. Confusion in clinical settings caused by inconsistent interpretation of the two terms

Even in the case where a "field action" should be taken, it is required to use the term "recall" in the public announcement. Due to the discrepancy between the term and the measures actually taken, confusion occurs in clinical settings.

ii. Extreme difficulty in promptly achieving a 100% recall/field action

There are some cases where it is extremely difficult to achieve a 100% completion of recall/field action the regulator requires because the company, despite its request, fails to obtain timely cooperation from medical facilities and other organizations involved and the company cannot communicate accurate information [to the end users] due to traceability issues[in its distribution channel].

iii. Impact on the market caused by thoughtless issuance of "recall" orders

Even thought a recall is voluntary, the regulatory authorities insists companies to recall a product unless safety is completely guaranteed, which is unrealistic because of limitation in manufacturing control and poses a risk of hampering the stable supply of the product.

iv. Interpretation of "field action" and ambiguity on its implementation

There is inconsistency in the interpretation of the concept of field action for large-scale devices, implantable devices, etc. In particular, there is no definitive interpretation of how field action (monitoring) should be conducted in the case of implantable devices, resulting in unclear methodology for field action and unclear responsibilities[23] for those involved, including healthcare professionals.

(2) Medical Device Reporting

The medical device reporting for malfunctions and infections is a mandatory reporting requirement for MAHs under the Pharmaceutical Affairs Law and following issues exist:

i. Manufacturers are uniformly required to submit a detailed report of each case and the same reporting deadlines as those for drugs are enforced, despite the fact that it is difficult to identify causes of defects and malfunctions due to their complexity and due to the diversity and characteristics of medical devices.

ii. A root cause investigation is sometimes required even for a known event. Such investigations for each case to identify causes pose a significant burden on companies. For the following reasons, there are many cases where the cause of a defect or malfunction can only be identified based on an assumption:

a) The specific cause of a defect is attributable to the skills of the doctor or another healthcare professional who used the device cannot be accurately elucidated.

b) In the case of implantable devices and other medical devices used by patients themselves, the information related to their privacy[24] cannot be often obtained due to lack of their cooperation.

c) In many cases, it is often difficult to deny any causal relationship between the device and the reported defect because accurate information on the use of a medical device by users themselves cannot be obtained.

iii. Due to the diversity of medical devices and skills required to use them, information described in a report is sometimes too difficult for PMDA staff to understand and additional time and personnel are required for answering to the questions and having hearings at PMDA.

[23] It is very likely that there are more than one effective method according to the characteristics of a device. Such methods include "field action" to remedy a problem on site and "monitoring" to be applied to products such as implantable devices for which physical removal is not always considered appropriate.

[24] Information such as patient's own living environment and habits

(3) How information should be provided

Providing doctors with information for safe and effective use of medical devices plays extremely important role. While cautions developed through risk management of the product and restriction of the usage are included in the package insert, it is very unlikely that doctors read the content of the package insert before using the device because the package insert itself is placed in a package along with the medical device. How the information should be provided still remain as a fundamental issue in terms of ensuring the accuracy and promptness in communication (sharing) of important information.

(4) Maintenance of medical devices

Maintenance are necessary for a medical device to maintain its performance for a designated period of time, some of those devices are designated as specified maintenance medical devices by the Minister for Health, Labour and Welfare, and companies using these devices are required to comply with strict regulations for their management and operation. Companies, as providers, secure resources required not only for providing the service manual and repair procedures but also for providing appropriate maintenance services, for example, by appointing technicians with expertise and highly specialized skills. Some medical institutions think that maintenance services are provided at free of charge after purchasing a medical device and it is sometimes difficult to gain their agreement that such services cannot be provided at free of charge. These institutions do not include costs of maintenance in the budget and, maintenance would not be conducted, as a result. Their limited budget may be a major factor but it cannot also be denied that they sometimes lack the awareness of the importance of maintenance[25]. It is thus absolutely impossible to expect their willingness to purchase a safer medical device to replace the old one.

2) Proposals for the aforementioned issues

To prevent the occurrence of defects/malfunctions associated with the use of a medical device and to promptly address a defect/malfunction that has occurred, it is necessary to create an environment where companies can identify the cause and address the problem and take prompt and appropriate countermeasures in the market under the postmarket regulations that accommodate the characteristics of the device. To achieve this goal, it is particularly necessary for companies and healthcare professionals to cooperate. The following are our specific proposals:

(1) Modernization of the concept of postmarket safety management and establishment of a system for product recall, field action, and monitoring

i. The concept of the postmarket safety management should shift from “a removal of a product even with the least possible risk from the market” to “a decision and implementation of appropriate measures by taking into account the degree of the impact of the defect/malfunction to the patient/healthcare professional, and urgency, etc.[26]” and improved methods for implementing recalls and field actions should be established.

ii. The terms “field action” and “recall” should be clearly defined and the definitions should be informed widely through the official notification system and at seminars, etc. Efforts should be made on promoting accurate understanding of the definitions among both companies and healthcare professionals.

[25] An accident in 2000 caused by the use of an artificial respirator that had failed to undergo periodic maintenance (an occurrence of a fire)

[26] Including the establishment of a process from a temporary suspension of use on the market while the root cause investigation is being conducted and to subsequent shipping discontinuation and recall/field action, establishment of a system to provide companies with consultation opportunities to discuss with the regulatory authorities measures to take with the possibility of stable supply and other factors taken into account, and establishment of a monitoring system to monitor the safety of implantable devices.

(2) Operation of a MDR system accommodating the characteristics of medical devices

In consideration of the difficulty in promptly identifying the root cause due to the diversity of medical devices and understanding the status of their use, we propose the operation as follows:

i. Those with full understanding of the medical device should be assigned to accept MDRs, consideration on the filed where the malfunction has occurred[27] should be given in identifying the root cause, and necessary consultation system should be established.

ii. In the current root cause investigation and follow-ups conducted on a case-by-case basis, the recipient of the report should avoid excessive demand and request only the minimum information necessary because each case has unique situation [and information available may vary]. An effective method to gather information should be established as well.

iii. Known defects/malfunctions and those for which countermeasures have been identified should be reported using a line list[28] and a report on each case should not be required.

iv. The regulatory authorities collaborate with the industry to promote the standardization of the terminology of defects to establish a system that realizes data analysis collected from different companies and a better environment to use medical devices through various measures, including education to healthcare professionals[29].

(3) How information should be provided

i. In consideration of the abundance of information on and the diversity of medical devices, unlike drugs, the common package insert format for drugs and medical devices should be reconsidered, and more visual means should be used to provide information, for example, electronically via the Internet, an instruction manual, or recording media such as CDs. The current package insert system should be reconsidered to incorporate more modern technology from the end users' point of view.

ii. Companies providing diagnostic devices, therapeutic devices, implantable devices, life support devices, and active implantable devices should abolish the uniform package insert placed in a product and improvement should be made in line with its original purpose: providing information. For example, reference materials provided separately from the product and warning materials should be prepared.

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[27] Since there is no legal obligation for users (physicians) to cooperate in providing detailed information that is necessary to understand how the device was used and in returning the product that caused the defect, there is a limit to what the reporter of the defect can do on its own. Even if any information is obtained, it is extremely difficult to identify a certain tendency regarding how individual users use the device.

[28] The US FDA has the Alternative Summary Reporting system that allows manufacturers to submit a summary report once in three months, if certain requirements are met, instead of individual MDRs.
(http : //www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072029.htm)

[29] Pharmaceutical and Medical Device Regulatory Science Research Project, Yokoi H. : Study on standardization and coding of the medical device defect terminology [in Japanese]

(4) Establishment of a new system to facilitate maintenance and inspection

i. Establishment of new requirements regarding maintenance and inspection that facilitate safe and effective use throughout the product life

ii. Implementation of maintenance and inspection of Specially Designated Controlled Medical Devices requiring maintenance and retention of its records

iii. Creating premiums on use of the medical devices, within their product life, that periodic maintenance and inspection are performed.

The current issues regarding postmarket safety management (GVP: Good Vigilance Practice) of medical devices and proposals to solve the issues described above are summarized in **Figure 14** below:

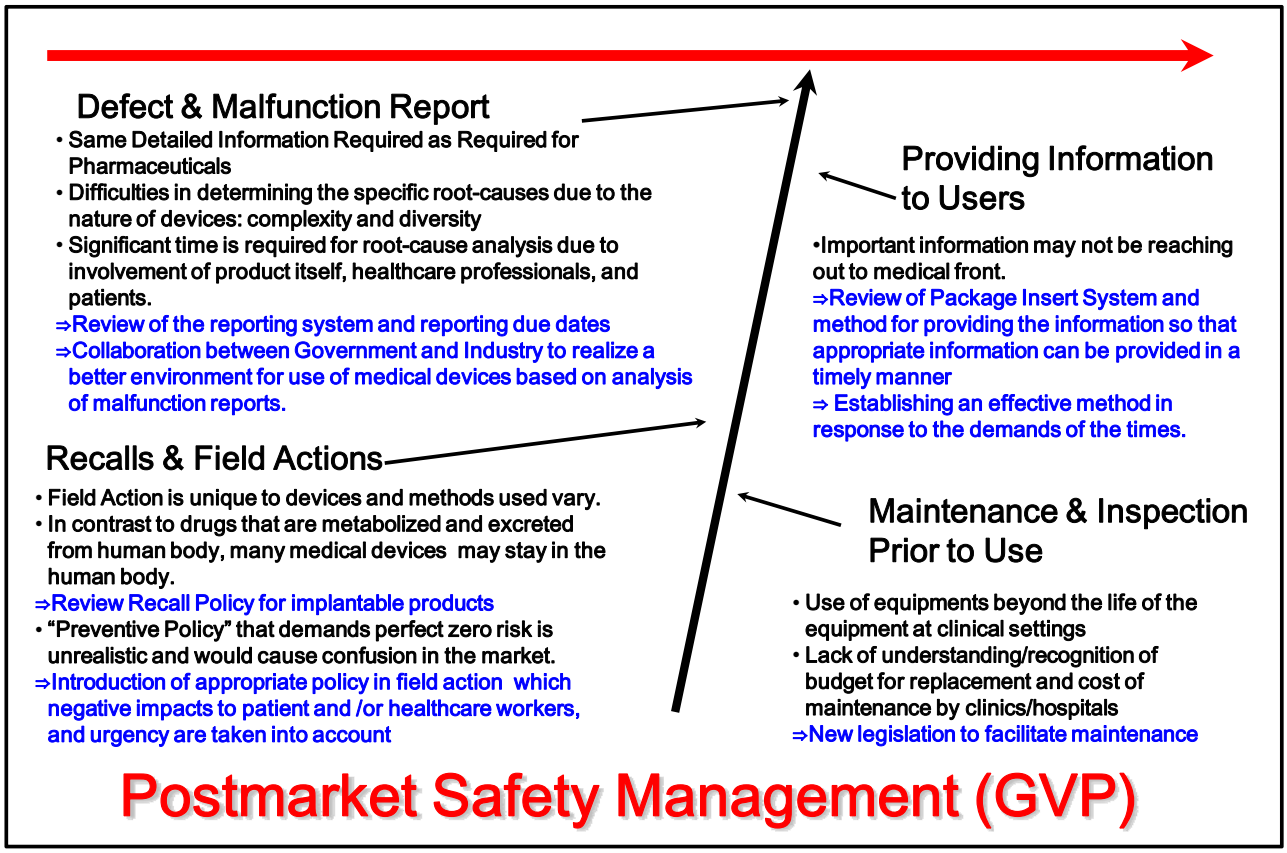

Figure 14: Issues and proposals regarding postmarket safety management of medical devices

Summary of proposals: It is necessary to introduce systems for "information provision," "medical device reporting" and "field actions" accommodating the characteristics and diversity of medical devices.

7. Business Licenses

One of the objectives of the revision of the Pharmaceutical Affairs Law (PAL) in 2005 was “revising the marketing approval system for international harmonization.” However, business licenses required under the PAL to market medical devices are significantly different from those regulated in other countries, causing serious problems in complying with the requirement in the trend toward international harmonization.

First of all, the QMS originally aims at managing the process seamlessly from design through to postmarketing and provides basic principles for how to manage each manufacturing site as manufacturers. To assess the efficacy of QMS, not just each manufacturing site but the entire company as a whole, as a manufacturer, should be the target of the assessment. It is important for the MAH to verify the efficacy of QMS of the entire company.

The business licenses are segmented into “sales,” “repair” and “manufacturing (cell-tissue-derived medical devices, sterilization, general, labeling.),” over which there is a market authorization holder (MAH), which has sole responsibility for launching medical devices on markets. There are, however, significant disparities between regulatory requirements for these licenses under the PAL, allowable scopes and responsibilities expected, and actual business practices. To address these disparities for maintaining and managing business licenses, many interpretations are made and significant resources and costs are wasted both by administrative agencies and companies.

1) Issues regarding business licenses for medical devices

(1) Application of Quality Management System (QMS): inappropriate adoption of QMS to manufacturers

QMS concerning manufacturing of medical devices consists both of software [management] and hardware [building and facilities], buildings and facilities adequate to manufacture the medical device are therefore included within QMS and are assessed in a QMS inspection. At present, however, in addition to product specific QMS inspection, inspection of buildings and facilities is performed at every manufacturing site, either on site or on paper, for manufacturing license (Foreign Manufacturer Accreditation). There is no consistency in QMS inspection.

QMS inspection on a product-by-product basis is performed every time the application for approval or certification of the product is filed. There are, therefore, cases in which different inspection authorities perform different inspections frequently according to different inspection procedures. This is irrational in terms of the effective use of resources of both inspectors and companies as well as of the effectiveness of inspection.

Particularly as for biological products, even manufacturing sites engaged in packaging process alone, which have relatively lower risk than those engaged in the entire manufacturing process, are uniformly covered by Article 2 of the MHLW Ministerial Ordinance No. 169 (QMS Ordinance), raising a concern that the hurdle to comply is too high for a low-risk process.

(2) Requirements to MAH license: confirmation of QMS compliance by manufacturers and information management from the market are not effective.

With regard to GQP and GVP requirements for MAHs, quality information and safety information, which both come from the market, are managed separately. Quality issues and safety issues are inextricably linked together. [From this aspect], it is not important to manage them separately. It is important to evaluate the information from quality and safety point of view and promptly provide the MAH with the outcome of the evaluation. The separation in the management process for quality and safety information will prevent [the MAH] from detecting early warning signs of quality issues, providing input to the process of corrective and preventive actions of the manufacturer, and implementing design changes if needed.

(3) Definition of manufacturing activities

i. Unclear regulatory interpretation of “rework prior to market release” within the business licenses scheme

As for medical device “instrument” manufactured at a foreign manufacturing site, if any defect/malfunction was identified at a facility licensed as a manufacturing site for labeling in Japan, the device is returned to the foreign manufacturing site for “rework.” This is because it is not clear in Japan which business license is required to conduct rework.

This return for rework poses a disadvantage to the user because he/she cannot use the product as scheduled due to the delay of delivery. This is also a serious problem in terms of a stable supply. In addition, the return may also damage the product and result in high costs.

ii. Unclear regulatory interpretation of “adding functions (upgrade, etc.) after market release” within the business license scheme

“Option” and “upgrade” (including hardware and software) that are developed and verified for post market installation and are provided along with the Installation Manual, and “upgrade” (including hardware and software) for improvement are not allowed at any of facilities that use the device, distribution channel, and Labeling, etc. manufacturers.

(4) Qualifications for business licenses: Balance between competency requirements and responsibilities required for a business license

i. General Controller of MAH

The qualifications for General Controller of MAH dealing with Specially Controlled Medical Devices or Controlled Medical Devices (Type I and Type II) specified in “Article 85, Paragraph 3, Item 1 of the Enforcement Regulations” are as follows:

“Those who completed a degree specialized in physics, chemistry, metallurgy, electricity, mechanics, pharmacy, medicine or dentistry, followed by three or more years’ experience in quality control, or postmarketing safety control of drugs or medical devices.”

This only describes academic and career requirements and raises a concern that an appropriate person with management ability, application ability, and decision-making ability as a manager responsible for marketing of medical devices may not be appointed due to lack of the qualifications required.

ii. Responsible Engineering Manager of Manufacturer

Of the following four categories of manufacturers specified by Article 26, Paragraph 5 of the Enforcement Regulations, activities of those in Category 4 have clearly lower risk than those in Category 1, 2, and 3. Despite these lower risk activities, the Responsible Engineering Manager of Manufacturer in Category 4 is required to have the same qualifications as those in other categories, raising a concern in terms of operation.

Category 1: Engaged in all or part of the manufacturing process of cell-tissue-derived medical devices, designated biological medical devices, and medical devices for certification purposes

Category 2: Engaged in all or part of the manufacturing process of sterile medical devices (excluding medical devices listed under Category 1)

Category 3: Engaged in all or part of the manufacturing process of medical devices other than those listed under Category 1 and 2

Category 4: Engaged in packaging, labeling or storage alone of the manufacturing process of medical devices listed under Category 2 and 3

iii. Responsible Supervisor for Manufacturing for Biological Medical Device

Manufacturer dealing with biological medical devices is required to assign the Responsible Supervisor for Biological Medical Device specified in the Article 68-2 of the PAL. The qualifications for the position are specified by "*Iyakuhatsu* No. 0515017-III-(5)-*a*." According to the provision, even manufacturers engaged only in packaging, etc., which have relatively lower risk than those engaged in the entire manufacturing process of biological medical devices, are required to appoint the Responsible Supervisor and the person needs to satisfy the same qualifications as those required for the position of manufacturers engaged in the entire manufacturing process of biological medical devices. It raises a concern in terms of operation.

2) Proposals for the aforementioned issues

With the aforementioned issues taken into account, the following proposals are provided to make business licenses more effective according to the characteristics of each medical device:

(1) Scope of QMS application

i. QMS should be implemented as follows in line with the concept of ISO 13485:

a) Define "manufacturer" as an operational entity of QMS and the MAH is responsible for confirming QMS compliance [at the manufacturer(s)].

b) Manufacturers whose conformity to QMS requirements has been verified should be exempted from "product specific QMS inspection" for every application of approval and/or certification.

c) If multiple manufacturing sites are managed under the same QMS, site specific QMS inspection is not necessary.

d) By mandating QMS compliance, the Manufacturing Licensing System and the Foreign Manufacturer Accreditation System should be changed to registration systems.

ii. GQP and GVP for MAH should be consolidated to make regulations more effective. Specific requirements should be as follows:

a) Control of release to markets
b) Internal audit
c) Training
d) Gathering, reviewing and evaluation of information from the market (input to the manufacturing site)
e) Field Action such as product recall
f) Confirmation of the manufacturer's compliance with QMS should be made based on an ISO 13485 certificate
g) Control of notifications for sales or lease of used products
h) Control of notifications for repair
i) Quality assurance at distributors or leasing companies
j) Control of documents and records (including additional requirements for biological medical devices)

In addition, instead of appointing Quality Controller and Safety Controller, pre-designated staff under the supervision of the General Controller may engage in activities concerned as requirements for MAHs.

iii. For manufacturers engaged in package, labeling, or storage only, Article 3 of the MHLW Ministerial Ordinance No. 169 (QMS Ordinance) should be applied uniformly, regardless of whether they deal with biological medical devices or not.

(2) Definition of manufacturing activities

i. Clarification of the position of rework prior to release under the business licenses

(Proposal 1)

"Engaged in packaging, labeling or storage only of the manufacturing process of medical devices listed under Section 2" specified in Article 26, Paragraph 5-4 of the Enforcement Regulations should be revised to "engaged in packaging, labeling or storage only, and rework only of the manufacturing process of medical devices listed under Section 2" in order to include rework in the same manufacturing category as packaging, etc. Requirements for the operational management of resources (human resource, infrastructure, etc.) that actually allow the company to be engaged in rework should be clarified separately in an Enforcement Notification, etc.

(Proposal 2)

"Those without approval for repair work on medical devices must not be engaged in repair of medical devices as business" specified in Article 40-2 of the PAL should be revised to "Those without approval for repair work on medical devices must not be engaged in repair of medical devices as business, regardless before or after release to the market" so as to include rework in the repair category.

(Proposal 3)

By allowing overseas manufacturing sites to make product release decisions for the market, rework of products of which product release decision has been made can be included in the scope of the repair business category according to “those without approval for repair work on medical devices must not be engaged in repair of medical devices as business” specified in Article 40-2 of the PAL.

ii. Clarification of the legal position for adding functions (upgrade, etc.) after release to the market under the business license scheme

Additions of functions (installation of options, upgrade, etc.) intended to be installed after release and “upgrade” (including hardware and software) for the purpose of improvement should be recognized as part of ancillary services and allowed to be provided along with the Installation Manual prepared by the MAH/manufacturer under the responsibilities required for those in the Sales License category.

(3) Qualifications for business license representatives

i. The qualifications for General Controller or equivalent should not simply be defined by the qualification of a pharmacist or academic background such as a degree from a specific discipline or department. Emphasis should be placed on selecting those who are deemed to have “competency” to fulfill the jobs specified in ISO 13485.

ii. As for the qualifications for Responsible Engineering Manager, the qualifications required for those in Category 4 (packaging and others) should be made less strict compared to those in Category 1, 2, and 3. In that case, those who are deemed to have “competency” to fulfill the jobs specified in ISO 13485 should be selected.

iii. As for Responsible Supervisor for Manufacturing for Biological Medical Device, Article 3 of the MHLW Ministerial Ordinance No. 169 (QMS Ordinance) alone should be applied uniformly to manufacturers engaged in package, labeling, and storage alone, regardless of whether they deal with biological medical devices so as not to require them to assign the Responsible Supervisor for Manufacturing for Biological Medical device.

The current issues regarding business licenses for medical devices and proposals to solve the aforementioned issues are summarized in **Figure 15**:

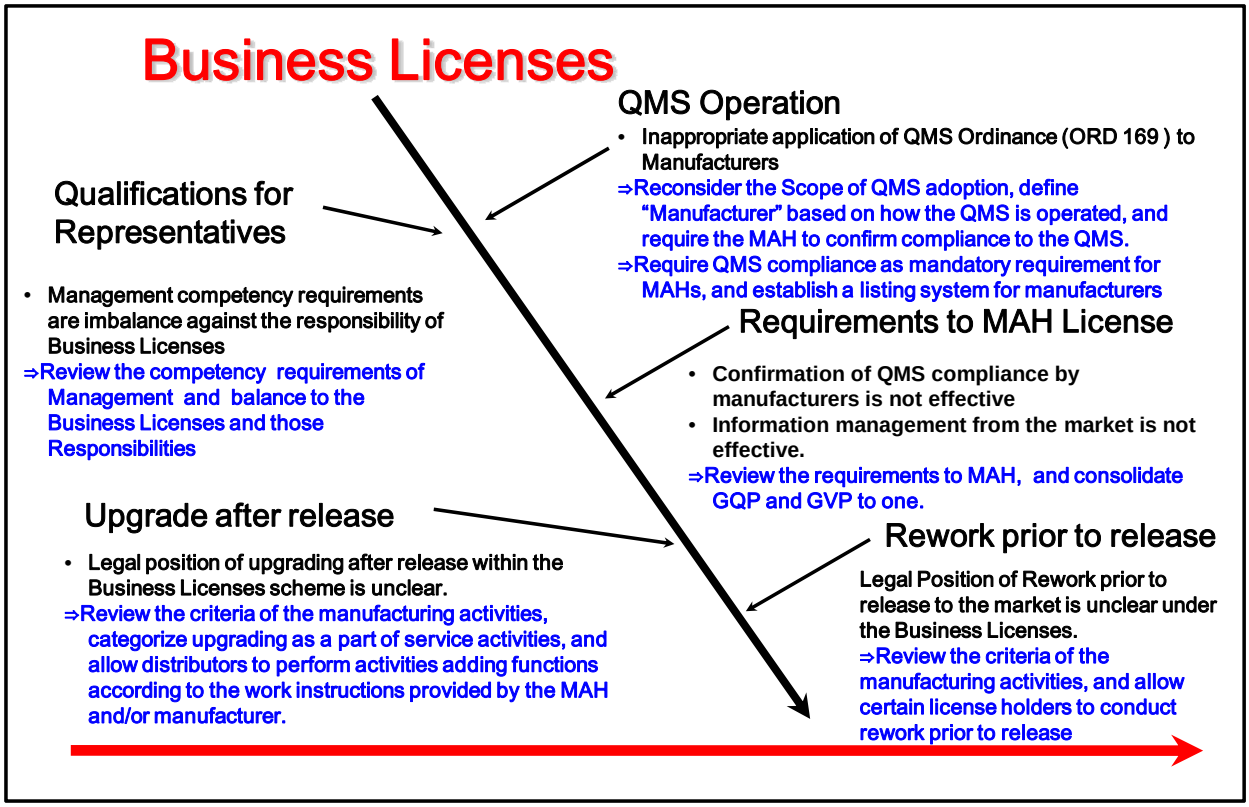

Figure 15: Issues and proposals regarding business licenses

Summary of proposals : To make business license scheme more effective and accommodating the characteristics of each medical device, QMS should be implemented in line with the concept of ISO 13485 (abolition of product specific QMS inspection upon application of approval and certification, shift of the manufacturing licensing and accreditation system to a registration system). To do so, the qualifications of those responsible for business licenses should be evaluated based on the "competency" to fulfill the jobs specified in ISO 13485.

In addition, since quality and safety are inextricably linked together, GQP and GVP should be consolidated because their separation would rather have negative effects. It is recommended, as an issue that needs particular consideration specific to medical devices, that legal rationales that allow rework before release and additions of functions (upgrade, etc.) after release be established.

Conclusion

--Toward establishing ideal Pharmaceutical Affairs Regulations--

The mission of the AMDD is to improve the welfare of patients in Japan by utilizing the latest medical technologies. To fulfill the mission, the RAQA Committee has been providing various proposals regarding issues concerning Pharmaceutical Affairs Regulation.

In the summer 2010, the leadership team of the RAQA Committee gathered on Awajishima Island. In our discussion throughout the night, we organized and analyzed, with the “Fish Bone Analysis Approach,” current situations and issues concerning Pharmaceutical Affairs Law, from the development phase to distribution phase of medical devices, with particular focus on differences between medical devices and drugs. As a result, we prepared a proposal statement presenting specific measures to fill the gap between the current situation and the desirable one.

While it has long been said that medical devices are different from drugs, no concerns over the application of the same regulations to both medical devices and drugs under the Pharmaceutical Affairs Law have been raised. Medical devices, which are manufactured by processing or assembling various parts, fall in the category of industrial products, such as automobiles and airplanes. Unlike drugs, it is impossible [for manufacturers] to control manufacturing and quality based on GMP requirements. The service and quality for medical devices are controlled by the Quality Management System (QMS) (ISO 13485 for medical devices) as the international standard. The mission of medical device companies is nothing but to commit them to implement postmarketing safety management based on feedback from the market and continuous improvement of products also based on feedback information. One of the major differences between medical devices and drugs is, as shown in the Fish Bone Chart in **Figure 16**, that while a drug completes its role after its active ingredient goes through the whole process once from start to end, the process of a medical device is a cycle that repeats almost eternally. This is why the management of this cycle is called “Total Product Life Cycle Management” in other countries. A medical device does not only last for one generation but will be inherited to the next generation.

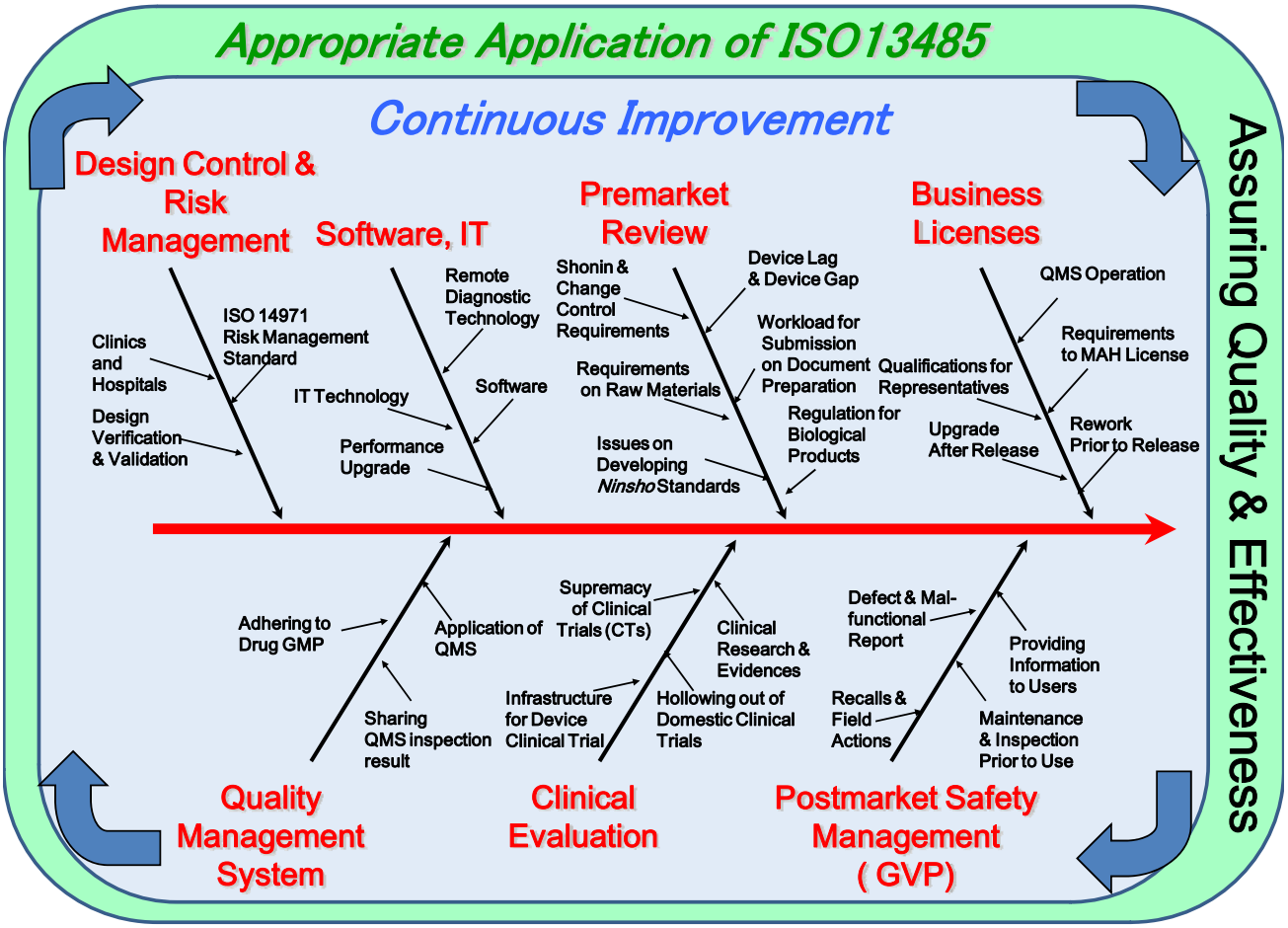

Figure 16: Quality and safety ensured for medical devices through continuous improvement

The differences between medical devices and drugs are significantly large. We therefore should understand the limitation and irrationality of the ongoing application of the same Pharmaceutical Affairs Law to these two different groups. The appropriate application of ISO 13485 would help improve postmarketing safety dramatically. We strongly believe that this will also make it possible to conduct a rational review of overlapping issues between the current product specific QMS inspection and approval review and, as a result, to introduce improved medical devices promptly to Japan. It is our hope to, at least, clear the stigma of Japan being labeled as a “market for clearing old inventory” as soon as possible.

It is our sincere hope that this proposal will be useful in allowing patients in Japan to access the latest medical technologies as quickly as those in other countries, in saving the lives of as many people as possible, and in providing a more comfortable and higher quality life to as many people as possible.

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